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ANNALS OF INTERNAL MEDICINE

VOLUME 29 AUGUST 1948 NUMBER 2

STREPTOMYCIN IN THE TREATMENT OF TUBERCULOSIS *

By J. BURNS AMBERSON, F.A.C.P., and WILLIAM H. STEARNS,
New York, N. Y.

THE effects of streptomycin administered to tuberculous patients have been shown to be strikingly beneficial in some phases of the disease, equivocal in some, and quite insignificant in others. Toxic damage by the antibiotic has been a frequent occurrence but this can be minimized by limiting the dose and the length of treatment. A more serious disadvantage, insurmountable thus far, is the development of bacterial resistance to streptomycin which often nullifies its further therapeutic action. While its potency against tuberculosis is unprecedented by any other drug, there are already some manifest limitations of its effectiveness. It has not altered the fundamental character of the disease to yield but stubbornly to treatment; nor that other subtle quality of seeming to yield for a time, only to relapse with renewed destructiveness. An important task, therefore, is to learn more of the limitations, which as yet are not precisely defined, so that streptomycin may be employed with maximum benefit at a critical point in the course of the disease.

A good many years are always required to determine the place of any treatment for tuberculosis, and streptomycin is no exception. Considering the short time since Waksman and his associates [1] announced their discovery and since Feldman and Hinshaw [2] demonstrated its therapeutic effects against tuberculosis, it is remarkable that so much knowledge of the drug has accumulated. This is in part due to the coöperative efforts of numerous investigators, hospitals and private and public agencies, including particularly the manufacturers of streptomycin, the American Trudeau Society, the Veterans Administration, and the National Institute of Health of the United States Public Health Service.

The purpose of this paper is to suggest some clinical interpretations which, although somewhat tentative, seem reasonable at this time. These

* Presented at the San Francisco meeting of the American College of Physicians, April 22, 1948.

From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Chest Service of Bellevue Hospital.

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are based on some knowledge of the work of others, particularly that of McDermott and Muschenheim [3] at the New York Hospital, and on two studies in which the authors are now participating, one in the Chest Service of Bellevue Hospital,* and the other in the Chest Section of the Medical Service of the Bronx Veterans Hospital.† The former is devoted mainly to an investigation of the effects of streptomycin in acute forms of tuberculosis (treatment has been completed thus far in 40 cases) while the latter is restricted to genitourinary tuberculosis (treatment completed in 25 cases). These studies will be reported in detail later. In addition, we have had experience with the drug in these hospitals, outside of the organized studies, in the routine care of patients.

In dealing with a disease as variable in its clinical manifestations as tuberculosis, it is not possible with precision to distinguish changes which occur in its natural evolution from those influenced by treatment; this is particularly true after the disease has become chronic. It was partly for this reason that we chose to study streptomycin in some cases of relatively early and severe acute disease. It is not always easy to evaluate the effects of streptomycin even in these, but at least some of the confusion met in more chronic cases that present both destructive and reparative lesions is avoided.

Symptomatic Response. When streptomycin exerts its maximum effect, patients suffering from acute febrile tuberculosis often experience a decided subjective change within three or four days, manifested by a feeling of well being and a return of energy and strength. This may antedate the subsidence of fever and may be associated with an improvement of appetite and the loss of other subjective evidences of toxemia. In a few cases high fever subsides abruptly, almost by crisis, within a week after treatment is started but in most there is a more gradual defervescence; this, however, is at a distinctly more steady and rapid rate than is usually observed under rest treatment alone. These patients, if previously malnourished and depleted, then may gain weight and, in the space of a few months, acquire an outwardly healthy, well nourished appearance. Nevertheless, a more sensitive indicator of toxemia, such as the erythrocyte sedimentation rate, may remain accelerated for several months after the disappearance of subjective symptoms.

The effect on local symptoms likewise is sometimes quite pronounced. Tuberculous laryngitis, causing severe pain and dysphagia, may respond so quickly that the patient is able to eat with little or no discomfort within several days to a week. Cough and expectoration often subside rapidly. In genitourinary cases there may be partial or complete relief of frequency, dysuria and other symptoms of bladder irritability. Such effects may be

* Supported by a contribution of streptomycin under the Streptomycin Manufacturers-American Trudeau Society Program, and by grants from the National Tuberculosis Association and the National Institute of Health.

† In coöperation with the Veterans Administration Streptomycin Committee. The urological observations were made by Dr. John K. Lattimer.

observed, of course, in the standard conservative treatment of tuberculosis, but under streptomycin therapy they are often more prompt and consistent.

Effect on Lesions. Relief from constitutional symptoms, such as fever, and sometimes also from local symptoms, usually occurs before any change in local lesions can be demonstrated; thus, the early cessation of the pain of tuberculous laryngitis may antedate any visible change in the appearance of the larynx. Presumably this is due to the retardation or arrest of active inflammatory edema, thus lowering the tension in the tissues and easing the irritation of sensory nerves. Within a few days to one or two weeks, if deep destruction has not already occurred, edema and redness of the laryngeal tissues may diminish, shallow ulcers may be seen to regress and in time the structures may assume a superficially normal appearance. Similarly, gross tuberculous inflammatory changes in the mucosa of the bladder may be observed cystoscopically to diminish, while its capacity increases toward normal. With respect to the lungs, a rather common manifestation of subsiding inflammation is the decrease of the purulence and daily output of sputum, while serial roentgenograms, taken at intervals of a few days to several weeks, often show rapid clearing of soft mottled shadows indicative of resolution.

This checking of active tuberculous inflammation and subsequent resolution of the inflammatory exudate is observed most strikingly in acute cases. When the response to streptomycin is prompt the rate of resolution is often definitely accelerated over that which would be expected under good rest treatment alone. When the duration of tuberculous pneumonia is only three or four weeks and a prompt arrest of the inflammatory process is induced by streptomycin, the subsequent resolution sometimes seems to be almost complete. The factor responsible for the resolution appears to be the suppressive effect of the antibiotic on bacterial growth before caseous necrosis has occurred.

Under rest treatment alone the tempo is slower, and caseation, therefore, is usually more extensive. However, the conclusion that complete resolution has occurred may be erroneous since we know that minute caseous foci may persist, invisible by roentgen-ray; sometimes the latter are betrayed by the persistence of fine râles after the roentgenogram shows virtually complete clearing.

In a number of cases of early tuberculous pneumonia there has been a prompt symptomatic response to the administration of streptomycin but a considerable lag in the resolution of the lesions; this proceeded then to a striking degree during two or three or more months after the completion of the streptomycin course. It is apparent, therefore, that the failure of lesions to resolve promptly is not necessarily an indication to continue the administration of the drug beyond the allotted time.

Lesions not Affected by Streptomycin. So far as the morphology of the lesion is concerned, we have learned that the extent of caseous necrosis,

which in turn depends upon the type and duration of the inflammation, limits to a great degree the response to streptomycin. Severe tuberculous pneumonia of two or three months' duration is usually widely caseous; there may be a temporary symptomatic response but with little or no demonstrable evidence of resolution and, in such instances, early relapse is probably to be expected. The same is true of caseous lesions in other sites. Tuberculous abscesses in soft tissues may persist as such. Nodular, presumably caseous, lesions in the epididymis and prostate usually do not show any striking change. This is not surprising in view of our fundamental knowledge that caseous lesions are organized slowly, with or without sloughing or ulceration. To what extent such healing is favored and accelerated after the use of streptomycin remains to be determined by some years of observation.

The presence of caseous lesions goes far to explain many observed phenomena. The frequent relapse and fatal course of tuberculous meningitis after an initial striking response to streptomycin therapy seems in some cases to be explained by the presence of caseous lesions in the cortex of the brain, which are the sources of renewed invasion of the meninges some time after the drug has had its effect. Similarly, streptomycin may promote temporary clinical recovery from generalized miliary tuberculosis and resolution of numerous non-necrotic metastatic lesions while the caseous focus of origin, perhaps invisible, remains little affected and may at a later date seed the blood stream again with a fatal result. In pulmonary cases, renewed progression of the disease by bronchogenic dissemination is more often related to persistent caseous foci containing viable tubercle bacilli than to any other single factor. Unless these residual necrotic lesions can be held in abeyance by prolonged and careful rest treatment to allow for the slow process of fibrous organization, relapse is almost inevitable.

However impressive may be the immediate effects of streptomycin, there is as yet no reason to think that the time required for the ultimate healing of residual caseous lesions and lasting clinical recovery is shortened; in fact, it may of necessity be lengthened. For example, initial recovery under streptomycin from acute progressive tuberculous pneumonia should be regarded only as a respite for the patient whose natural resistance failed to cope with the infection; a favorable balance can be restored but slowly, if at all. He should have perhaps a year or more of bed rest, and another year or so of convalescent care in order, as far as possible, to promote permanent recovery.

Caseous necrosis, as a rule, is not as deep and massive in canalicular structures such as the larynx, bronchi, intestine and bladder, as it is in visceral tissues. Logically, therefore, it might be supposed that tuberculosis in the former would be more accessible to the action of streptomycin, and this seems to be borne out by the observations. The prompt improvement of lesions here, as well as in the skin, is on the average more striking than it is in deeply involved viscera such as the lungs or the kidneys.

Even though ulcerated caseous lesions are sometimes affected little, if at all, by streptomycin, the exudation and discharge from them may be at

least temporarily diminished, as indicated, for instance, by an improvement in the amount and character of the sputum or in the degree of pyuria. Such changes are frequently observed without any appreciable difference in the size of the pulmonary cavity or the renal defect. Nevertheless, even a partial control of purulent exudation may be a desirable thing, particularly to help avoid further dissemination of the infection through the bronchi in the case of the lung, or through the ureters in the case of the kidneys. This may help prepare the way for other needed treatment such as artificial pneumothorax or surgical intervention. On the other hand, the disappearance of tubercle bacilli from the sputum or the urine may be misleading, since this is not good evidence of healing unless there is also a simultaneous obliteration of the ulcerated lesions from which the organisms were discharged.

In several cases of tuberculous pneumonia we have observed the lesions to break down and excavate rapidly during the course of streptomycin treatment. In spite of this, new bronchogenic lesions were not demonstrated. Here, it would seem, we observe in a patient with poor native resistance a temporary prevention of new inflammation without any control of older necrotic foci.

The Importance of Vital Resistance. Almost all who have studied the effects of streptomycin recognize the importance of vital resistance in the final issue of the case. It is well known that the identification of the factors involved is uncertain and relatively crude. We appreciate the relationships of age, sex, race, and state of nutrition, but beyond this we are obliged to rely only upon judgments which often are much more intuitive than scientific. Brief experience, however, seems rather clearly to indicate that relapse after streptomycin treatment is relatively more frequent in those with poor native resistance and that this occurs earlier and with greater severity. The implication is clear, therefore, that in such cases facilities should be available for long and rigid rest treatment, perhaps aided by collapse therapy, in order to gain the most from any temporary benefit of the drug.

Drug Resistance. As Muschenheim has reasoned, it would be desirable theoretically to administer a drug like streptomycin during many months to obtain lasting benefits from its antimicrobial effects. This would be obligatory were it not for the development of drug resistance among tubercle bacilli.

The studies of Steenken,[4] McDermott,[5] Youmans,[5] and others have shown that resistant variants of the bacillus are recognized in cultures of sputum or other exudates within four weeks of the start of treatment and that such resistance becomes more frequent the longer treatment is continued; after three to four months 70 per cent or more of the patients harbor bacilli with resistance so strong that the usual therapeutic doses of the drug are no longer effective. The development of resistance seems to be more closely related to the duration of treatment than to the daily dose employed. Cumulative evidence suggests that bacterial resistance, once developed, may well be permanent. In many cases this accounts for the failure of streptomycin

to have any further effect even though the initial benefit may have been striking. However, there is some evidence that strains of varying resistance occur in different lesions in the treated patient and that in such cases a renewed dissemination of sensitive bacilli may be controlled by retreatment with streptomycin. Because of these observations a number of studies are under way to determine the optimum dosage of the drug and the optimum time of administration. Our own investigation of 40 cases of acute tuberculosis, 18 treated with 2 grams of streptomycin daily, and 22 with 1 gram daily for 42 days, indicates that this relatively short period may be as effective in some instances as a longer period of administration. In these regimens, development of drug resistant variants is approximately 25 to 30 per cent, including a number of cases in which drug resistance has continued to increase after the termination of treatment. Such a regimen, therefore, provides a possible therapeutic leeway for retreatment should the first course of the drug prove to be inadequate. It also has the advantage that patients who, after a period of rest cure, require surgical intervention for the tuberculosis, may then expect some protection and benefit under a renewed course of streptomycin.

Toxicity of Streptomycin. The toxic effects of the drug in human beings have been described by Farrington et al.[6] The damage of the labyrinthine apparatus is the most common and serious when the drug is administered in high dosage for long periods of time. Our study of relatively smaller doses for six weeks indicates that 1 gram of the drug a day does not destroy vestibular function, as shown by caloric tests, although there may be occasional partial impairment. By contrast, 2 grams daily for the same period has caused complete loss of function in 12 of the 18 cases treated. The damage is persistent and presumably permanent, although the patient may be able to compensate. It should be emphasized that complete loss of this function, as determined by caloric tests, may occur although the patient may experience no vertigo or other symptoms so long as he remains in bed.

Schedule of Treatment. Because of possible toxic effects of streptomycin and the high incidence of drug fastness after three to four months of treatment, an effort has been made to obtain the therapeutic effects with 1 to 2 grams of the drug daily for six weeks. In acute pneumonic cases 1 gram seems to us to be as effective as 2 grams. More study will be required to determine the optimum regimen which will probably vary from case to case. It seems important not to exhaust the effectiveness of the drug during the initial course of treatment unless the indications are very urgent.

In desperate cases of tuberculosis such as generalized hematogenous miliary tuberculosis and tuberculous meningitis, where the termination under ordinary conditions is usually fatal in a few weeks or several months, we are in agreement with many others that the disadvantages of drug toxicity and bacterial resistance should be ignored and that streptomycin should be administered intramuscularly in daily doses totalling 40 mg. per kg. body weight (2 gm./110 pounds) for a period of 90 days. In addition, in menin-

gitis, 50 mg. should be given intrathecally at 24 to 72 hour intervals during the 90 days. In most cases there will be at least a temporary remission of the disease although relapses occur at a rate which, in the case of meningitis, is exceedingly high; i.e., approximately 80 per cent fatality. In these situations, the reports of Lincoln and her associates [7] suggest that the addition of promizole may be beneficial. The place of the sulfones, para-aminosalicylic acid and other agents, as supplements to streptomycin, can be established only by further investigation.

In cases of acute tuberculous pneumonia known to be of short duration (two to four weeks) benefit can usually be expected with 1 gram of streptomycin, intramuscularly, daily for a course of six weeks. If, after a short interval, the symptoms recur and the disease progresses, retreatment is sometimes effective. If the tuberculous pneumonia is of longer duration and presumably extensively caseous, a longer period of continuous treatment is probably justified, although it is questionable whether larger doses will prove to be more effective. In these cases the incidence of relapse can be expected to be high and eventually no further effect can be anticipated from streptomycin.

In milder cases, if streptomycin seems indicated at all, there is strong reason to use small doses for relatively short periods of time. This should probably not exceed 1 gram a day for six weeks and in many cases the course could well be terminated earlier than six weeks if the desired effect is being approached. Such a regimen may achieve limited goals such as the improvement of a bronchial lesion or the closure of a cutaneous sinus. In every case, a careful evaluation of the situation should be made particularly to prognosticate whether more critical episodes might arise in the future. If so, it may be wise to withhold streptomycin; in other words, use light arms for minor engagements and save the heavy artillery for the crucial battles ahead. For the reasons stated, it is generally agreed that patients who may be expected to respond to conventional rest treatment should not be treated with streptomycin even though this might accelerate early symptomatic improvement.

Deductions

Until more experience accumulates, any deductions must be qualified. At the moment, however, the following interpretations of some of the evidence seem reasonable:

The effects of streptomycin in tuberculosis are most evident in promoting the control of acute inflammatory changes, presumably by the arrest of bacterial activity. In recent lesions of this character, the effect may be prompt and striking and may help to avoid extensive caseous necrosis, may relieve the heavy demands on the patient's vital resistance and may provide a respite during which the natural processes of healing may be initiated. A continuation of rest treatment is necessary then to further the healing which, at best, is very slow.

The early favorable effects of streptomycin in acute disease may be of short duration because of low native resistance, extensive caseous necrosis and the development of bacterial resistance against the drug. Relapse will probably be more frequent in such cases responding to streptomycin than in acute cases which respond favorably to rest treatment alone.

In chronic tuberculosis streptomycin may be used for limited and well defined purposes but it should not be administered to the point of ineffectiveness for relatively trivial episodes.

Streptomycin should be administered for a prolonged time, regardless of anticipated toxic effects and bacterial resistance, in desperate forms of the disease, detected early; i.e., acute generalized hematogenous tuberculosis and tuberculous meningitis.

In less urgent situations, the length of the course of treatment and the daily dose of the drug should be limited if this seems likely to be adequate.

Phases of tuberculosis which may be expected, according to experience, to respond well to good rest treatment should not be treated with streptomycin.

In any case a careful and complete evaluation of the actual and potential status of the disease should be made to determine the wisdom of administering streptomycin, holding it in reserve, or relying wholly on conventional rest treatment.

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THE URINARY EXCRETION OF RADIOACTIVE IODINE AS AN AID IN THE DIAGNOSIS OF HYPERTHYROIDISM *

By JANET W. MCARTHUR, M.D.,† RULON W. RAWSON, M.D., REX G. FLUHARTY, and J. H. MEANS, M.D., F.A.C.P.,
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THYROTOXICOSIS, in its classical form, is one of the most readily recognizable of all the diseases in medicine. In atypical form, however, hyperthyroidism may present formidable diagnostic difficulties. A growing number of laboratory aids have been devised to reduce the number of undiagnosed borderline cases, characterized by nervousness combined with a persistently elevated metabolic rate, which plague every thyroid clinic.

Among these auxiliary diagnostic technics is the so-called "iodine tolerance test," designed to appraise the functional activity of the thyroid gland by measurement of its capacity to take up iodine. Experimental precedent for this test derives from the classic perfusion experiments of Marine and his associates [1, 2] who demonstrated the selective affinity of the thyroid gland for iodine. Hyperplastic glands, with a low iodine content, were shown to remove the largest quantities of iodine from the perfusion fluid.

Clinical determination of iodine tolerance has been attempted in a number of ways: (*a*) Measurement of the rate and completeness of disappearance from the blood stream of a calculated amount of iodine administered to the patient.[3, 4, 5, 6, 7] The blood iodine curve of the thyrotoxic patient whose thyroid is avid for iodine does not show the peak which characterizes the curve of the normal or non-toxic goitrous individual; the whole curve lies below the arbitrary limit of normal. A disadvantage to this technic is that it requires multiple determinations of the level of blood iodine, an intricate laboratory procedure. (*b*) Direct determination of the uptake of radioactive iodine by external gamma ray measurements on the thyroid in situ with the Geiger-Müller counter.[8, 9] By this method, certain patients with classic Graves' disease appeared to be distinguishable from patients with hyperophthalmopathic Graves' disease and from normal individuals by their greater uptake of labelled iodine. The error in this type of measurement is in all likelihood appreciable, owing to individual variations in the size and anatomical position of the thyroid and, during the initial phases, to the background of radioactivity in the patient's body. (*c*) Quantitation of the iodine excreted in the urine during a given period of time after the administration

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† Henry P. Walcott Fellow.
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of a standard dose of iodine. Chemical methods for determining the urinary iodine excretion have been employed for this purpose by Elmer,[10] Watson [4, 5] and by Perkin, Brown and Lang.[3] Disadvantages of this technic are the difficulty of the analytical procedure and insensitivity of the method due to the fluctuant level of excretion of dietary iodine and the consequent necessity for administration of a relatively large test dose of iodine.

The precision and ease with which the urinary excretion of iodine can be determined has been greatly enhanced by the introduction of the radioactive isotopes of iodine. Moreover, a dynamic conception of iodine metabolism can be gained since the iodine administered in the test dose becomes distinguishable from iodine already present in the body. Physical methods

TABLE I

The Urinary Excretion of Iodine Administered to Euthyroid and Hyperthyroid Individuals as Reported by Various Investigators

Author	Dose of Iodine	Route	Urinary Iodine Excretion				
			No. of Patients	Type of Patients	Average	Range	Period of Urine Collection
Elmer[10]	1300 gamma	Intravenous	19 9 3 6	Euthyroid Hyperthyroid Severe Mild	16.6% 15.6%	11.7–20.5% 0.8–24 % 0.8–24 14.0–21	6h
Hertz and Roberts[8]	<2 mg. Labelled with radioactive iodine	Oral	1 6 6	Euthyroid Hyperthyroid Ophthalmopathic Graves' disease	63.0% 25.0% 46.0%	10.0–37 % 32.0–56 %	72h
Watson[5]	250 gamma/kilo	Intravenous	24 27	Euthyroid Hyperthyroid	552 gamma 403	44–1396 gamma 30–1734	6h
Hamilton and Soley[9]	14 mg. Labelled with radioactive iodine	Oral	6 1	Euthyroid Hyperthyroid (toxic nodular goiter)	83.5% 84.6%	76.0–88 %	5d
Perkin, Brown, Lang[3]	75 mg.	Oral	7 9	Euthyroid Hyperthyroid	20.6% 12.8%	10.3–25.7% 4.2–15.5%	24h

for measuring the urinary excretion of radioactive iodine have been utilized in a small group of patients by Hertz and Roberts.[8] A possible objection to the radioactive tracer method is that the presence of the radiation may alter the physiological properties of the tissues under investigation. While this contingency seems unlikely in view of the great dilution of the radioactive element, experimental study directed toward resolution of the difficulty is in progress in this laboratory.

In table 1 is summarized the urinary excretion of iodine administered to euthyroid individuals and to patients with untreated hyperthyroidism, as

reported by the various investigators cited above, together with the dose of iodine employed and the route of administration. These data have seemed to us sufficiently promising to warrant further investigation. We have attempted to evaluate the clinical usefulness of the measurement of radioactive iodine excretion by defining more precisely the range of excretion to be anticipated in non-thyrotoxic individuals and in patients with hyperthyroidism.

TABLE II

Clinical, Metabolic and Radioactive Iodine Excretion Data for the Non-Thyrotoxic Group

A. Patients initially suspected of having Graves' disease

Case No.	Complicating Diseases	Extent of Thyroid Enlargement	48 Hour RaI Excretion (%)	Activity of Tracer (Microcuries)	Dose of Iodide (gamma)	B.M.R.
1	Pregnancy	1½ × N size	36	100	2.4	+11
2	Arteriosclerotic heart disease	——	44	100	2.0	+20
3	Nodular goiter	2 × N size	85	100	5.0	+ 7
4	Nodular goiter	2 × N size	54	100	3.3	+ 3
5	——	——	38	100	8.0	+ 8
6	Anxiety neurosis	——	71	200	100.0	+ 2
7	Alcoholism, chronic hepatitis	——	43	100	5.5	+22
8	Chronic rheumatic heart disease	2 × N size	92	100	4.0	+18
9	Hypertensive cardiovascular disease, nodular goiter	2 × N size	52	100	2.4	+ 5
10	Hypertensive cardiovascular disease, Parkinsonism	——	56	100	4.0	+32
11	Bronchial asthma	——	36	100	3.2	+26
12	Nodular goiter	1½ × N size	32	100	5.0	+ 7
13	Hypertensive cardiovascular disease, anxiety neurosis	1½ × N size	50	100	3.2	+ 2
14	Pheochromocytoma	——	40	100	40.0	+65
15	Thyrotoxicosis factitia	——	98	300	100.0	+52
16	Hypertensive cardiovascular disease	1½ × N size	89	100	100.0	+37
17	Obstructive jaundice, nodular goiter	2 × N size	43	50	50.0	+28
18	Hypertensive cardiovascular disease	——	98	100	100.0	+20

B. Patients given radioactive iodine for other research purposes

19	Chronic lymphatic leukemia	——	50	100.0	10.0	+ 7
20	Acute lymphatic leukemia	——	53	100.0	10.0	—
21	Chronic lymphatic leukemia	——	59	100.0	60.0	+ 2
22	Metastatic carcinoma cervical nodes	——	76	100.0	34.0	—
23	Fetal adenoma of thyroid	Single nodule	38	1000.0	60.0	− 4
24	Struma nodosa and papillary adenocystoma of thyroid	Single nodule	58	2000.0	200.0	+ 2
25	Papillary adenocystoma of thyroid	Single nodule	83	1000.0	34.0	—
26	Struma nodosa of thyroid	Single nodule	63	1000.0	160.0	0
27	Hurthle cell tumor of thyroid, benign	Single nodule	51	1000.0	54.0	− 7
28	Colloid adenoma of thyroid	Single nodule	65	1000.0	100.0	− 9
29	Papillary carcinoma of thyroid	Single nodule	71	1000.0	100.0	− 1
30	Papillary carcinoma of thyroid	Single nodule	74	800.0	16.0	−19

Methods and Materials

Tracer doses (2 to 160 gamma) of sodium iodide labelled with radioactive iodine (I^{131}) whose specific activity varied from 50 to 2000 microcuries (in the majority of instances the activity was 100 microcuries) were administered orally to patients. Urines were collected for 48 hours following the administration of the labelled iodine, and the percentage excretion determined from the specific activity of an aliquot. A number of seemingly toxic patients had no palpable goiter. To these individuals a dose of radioactive iodine was administered and the entire body searched for iodine-concentrating tissue 24 to 36 hours later with the Geiger counter.

The non-thyrotoxic group comprised 30 cases. Of these, 18 were initially suspected of having hyperthyroidism. The diagnosis of thyrotoxicosis was finally excluded in these patients after prolonged study and observation.

Table III

Clinical, Metabolic and Radioactive Iodine Excretion Data for the Thyrotoxic Group

Case No.	Type and Size of Goiter	Complicating Diseases	48 Hour RaI Excretion (%)	Activity of Tracer (Microcuries)	Dose of Iodide (gamma)	B.M.R.
1	Diffuse, 2×N	Hypertensive cardiovascular disease	30	173	5.0	+54
2	Diffuse, 3×N	——	39	100	10.0	+22
3	Diffuse, 1½×N	Duodenal ulcer, ovarian tumor	21	300	100.0	+23
4	Not palpable	——	30	184	8.6	+23
5	Diffuse, 2×N	Thyrotoxic myopathy	18	100	32.0	+60
6	Diffuse, 3×N	——	15	100	15.0	+42
7	Diffuse, 2½×N	Anxiety neurosis	26	100	100.0	+55
8	Nodular, 2×N	——	38	100	100.0	+25
9	Nodular, 2×N	——	15	100	100.0	+24
10	Diffuse, 2×N	——	19	100	5.5	+20
11	Nodular, 2×N	——	22	1730	44.0	+32
12	Diffuse, 1½×N	——	8	100	4.5	+61
13	Diffuse, 3½×N	——	16	250	150.0	+37
14	Diffuse, 2×N	——	31	100	2.4	+13
15*	Diffuse, 2×N	——	23	100	4.0	+27
16*	Nodular, 3×N	——	15	100	150.0	+41
17*	Diffuse, 2×N	——	32	100	100.0	+42
18	Diffuse, 1½×N	Rheumatoid arthritis	35	100	100.0	+32
19	Nodular, 1½×N	Rheumatoid arthritis	26	100	100.0	+48
20	Diffuse, 2½×N	Lung malignancy	7	100	100.0	+55
21	Diffuse, 2×N	Rheumatoid arthritis	38	100	100.0	+46
22	Diffuse, 2×N	——	45	100	100.0	+26

* Persistent thyrotoxicosis after radioactive iodine therapy.

Eleven were patients with non-metabolic diseases given radioactive iodine for some other research purpose. Table 2 summarizes the diagnoses in these patients, together with the basal metabolic rate, urinary excretion of radioactive iodine, and the iodide content and specific activity of the administered tracer. The last eight patients in the table were individuals operated upon for the removal of a single nodule of the thyroid. Only those cases in whom the tumor tissue was shown to be non-functional by failure to take up radioactive iodine have been included.

The thyrotoxic group consisted of 22 cases of classic untreated * Graves' disease. Table 3 presents the clinical, metabolic and excretion data for these patients.

Results

The mean radioactive iodine excretion by the 30 non-thyrotoxic patients was 60 per cent, range 23 per cent to 98 per cent. The mean excretion by the 22 thyrotoxic patients was 25 per cent, range 7 per cent to 45 per cent. The extent of overlapping may be gauged from the histogram (figure 1).

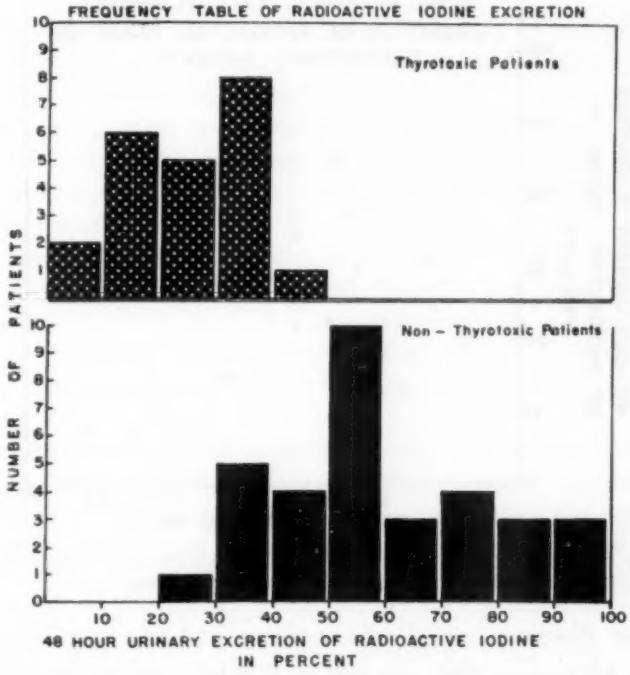

FIG. 1. The histogram showing frequency distribution of 48 hour urinary excretion of radioactive iodine in per cent in thyrotoxic and non-thyrotoxic patients.

As shown by the scatter diagram (figure 2), there is a small negative correlation between the radioactive iodine excretion and the basal metabolic rate in thyrotoxic patients.

Specifically, the finding of a low urinary excretion of radioactive iodine aided in establishing the diagnosis of thyrotoxicosis in patients 3 and 9 (table 3). These were individuals in whom a diagnosis of hyperthyroidism could not be made with assurance clinically. The anatomic changes observed in the operatively removed thyroids and the symptomatic improvement with gain in weight by these patients following thyroidectomy leave little doubt as to the preëxistence of toxicity.

* Three patients had thyrotoxicosis persisting after radioactive iodine therapy.

The finding of a high urinary excretion of radioactive iodine facilitated the exclusion of hyperthyroidism in cases No. 2, 6, 7, 8, 9, 10, 13, 14, 17, and 18 (table 2). These were patients in whom features of the history or clinical appearance were suggestive of thyrotoxicosis. A persistently elevated basal metabolic rate and an equivocal response to a therapeutic test with iodine further confused the diagnosis in a number of instances. One patient was a chronic alcoholic; two had anxiety neurosis; one had compensated arteriosclerotic heart disease; four, compensated hypertensive

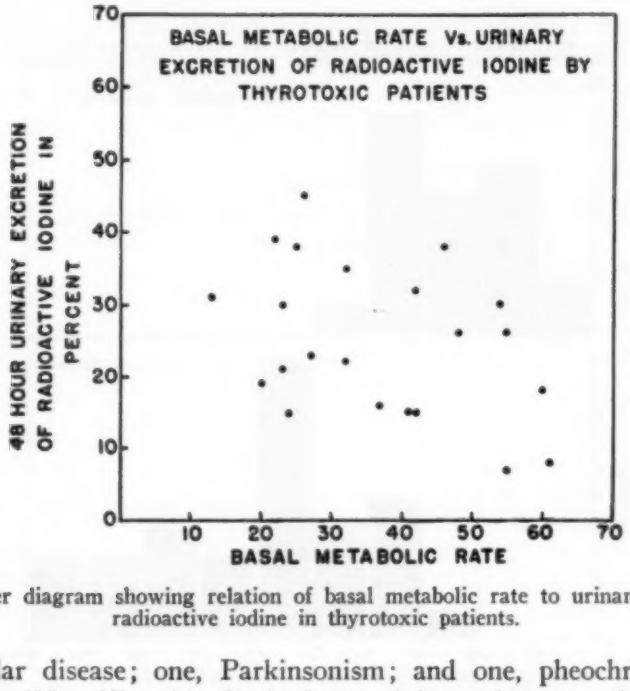

FIG. 2. Scatter diagram showing relation of basal metabolic rate to urinary excretion of radioactive iodine in thyrotoxic patients.

cardiovascular disease; one, Parkinsonism; and one, pheochromocytoma. One patient (No. 17, table 2) had a nodular goiter, an elevated basal metabolic rate and an elevated blood iodine due to a cholecystogram done some months previously.

Survey of the body with the Geiger counter yielded important information in two toxic patients in whom no thyroid tissue could be palpated in the neck. Case No. 15 (table 2) was that of a female patient who had undergone subtotal thyroidectomy for Graves' disease 10 years before admission. Two fruitless explorations of the neck had been done subsequently at an outside hospital for "recurrent thyrotoxicosis." At entry, the patient presented the classic appearance of Graves' disease except for the absence of goiter. *Struma ovarii* was suspected because of slight enlargement of the right ovary. Search with the Geiger counter disclosed no iodine-concentrating tissue anywhere in the body, and virtually the entire tracer dose of iodine was excreted within 48 hours. The diagnosis of thyrotoxicosis *factitia* was confirmed by the finding of tablets of desiccated thyroid in the patient's possession and by

the rapid fall in the basal metabolic rate and the serum protein-bound iodine upon withdrawal of this desiccated thyroid.

Case No. 4 (table 3) was that of a male patient with moderately severe thyrotoxicosis in whom the propriety of exploring the neck was debated because of the absence of palpable thyroid tissue. Heavy external gamma radiation from the cervical region was detected by the Geiger counter after the administration of radioactive iodine, and at operation a small quantity of hyperplastic thyroid tissue, weighing 19 gm., was found.

Discussion

The proportion of a test dose of iodine excreted in the urine within a given time is dependent upon: (1) the avidity of the thyroid gland for iodine, and (2) a variety of extrathyroidal factors, among which are the quantity and type of iodine compound administered, the rate of absorption of iodine, and the state of kidney function. When radioactive iodine is employed the existence of the radioactivity may influence the physiological processes under study.

An increased avidity for iodine is possessed by hyperplastic thyroid glands with a low iodine content from any cause.* Confirmation of this fact has been obtained with radioactive tracer technics both in experimental animals [11] and in patients.[9, 12] The existence of clinical hyperthyroidism is therefore not a necessary corollary to the demonstration of increased iodine tolerance.

Among the extra-thyroidal factors affecting the urinary excretion of a test dose of iodine, it is clear that the quantity of iodine administered is of major importance. The percentage of iodine collected by the normal thyroid varies inversely with the size of the dose.[3] In previously untreated patients with Graves' disease, the initial collection of iodine has been reported to approximate 100 per cent for small doses (0.2 to 5.0 mg.) while the initial collection from larger doses is considerably smaller.[14] The dosage factor doubtless accounts, in part, for the magnitude of the difference in urinary iodine excretion between euthyroid and hyperthyroid individuals reported by the various investigators in table 1. Administration of the smallest possible dose of iodine compatible with accurate measurement would seem to promise optimal sensitivity.

Since all of the iodine tolerance procedures have employed iodide as the test substance, the type of iodine compound administered can be neglected.

The rate of absorption of iodide from the gastrointestinal tract of normal individuals is extremely rapid. The blood iodine concentration reaches its peak within 30 minutes when doses of 2 gm. or more of potassium iodide are ingested.[15] The peak is not attained until 90 minutes after the ingestion of 0.5 gm. of potassium iodide.[16] Radioactivity is detectable in the hand within three to six minutes after the ingestion of 250 mg. of sodium iodide labelled

* Unless iodine uptake be blocked by an agent such as thiouracil.

with radioactive iodine and absorption is apparently complete within three hours.[17] Precise data regarding the absorption of the very much smaller doses of iodide administered in these iodine tolerance tests are not available.

The state of renal function may significantly affect the excretion of iodide. According to Salter,[18] the urinary excretion of an administered dose of iodine is retarded in patients with renal damage. Inasmuch as experimental passive congestion of the kidneys has been shown to retard the excretion of iodine,[19] the urinary excretion test is presumably invalid in the presence of cardiac decompensation.

The low correlation found between the urinary excretion of radioactive iodine and the basal metabolic rate in thyrotoxic patients merits particular comment. That only one component of the basal oxygen consumption is ascribable to thyroid activity has long been known. It seems clear that the iodine tolerance test is not measuring precisely the same function as the metabolic rate. Which measure of thyroid function possesses the greater intrinsic validity cannot be deduced from the facts currently available. The low correlation between the two variables proved clinically advantageous in a number of instances (cases No. 3, 9, 19, and 23, table 3). These were patients in whom the elevation of the basal metabolic rate was minimal but in whom the low urinary excretion of radioactive iodine provided decisive evidence for the presence of thyrotoxicosis.

Conclusions

1. The mean urinary excretion of radioactive iodine by 22 thyrotoxic patients was 25 per cent, range 7 per cent to 45 per cent.

2. The mean urinary excretion of radioactive iodine by 30 non-thyrotoxic patients was 60 per cent, range 23 per cent to 98 per cent.

3. There is considerable overlapping in the radioactive iodine excretion between thyrotoxic and non-thyrotoxic individuals in the range 20 to 40 per cent.

4. The finding of a low urinary excretion of radioactive iodine aided in establishing the diagnosis of Graves' disease in clinically equivocal cases. The finding of a high urinary excretion of radioactive iodine was of assistance in excluding Graves' disease in borderline cases in whom a truly basal metabolic rate could not be obtained. Specifically, the exclusion of Graves' disease has been facilitated in patients exhibiting hypermetabolism due to alcoholism, anxiety, compensated hypertensive cardiovascular disease, Parkinsonism, pheochromocytoma and thyrotoxicosis factitia. In that group of patients exhibiting an intermediate (20 to 40 per cent) excretion of radioactive iodine, the diagnosis of Graves' disease must be established by other clinical and laboratory findings.

5. Search for external gamma radiation with the Geiger-Müller counter following the administration of a tracer dose of radioactive iodine enables the location of thyroid tissue to be established when doubt exists.

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PATHOGENESIS OF HUMAN BRUCELLOSIS WITH RESPECT TO PREVENTION AND TREATMENT *

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MEDICAL historians have informed us that brucellosis is a disease of antiquity, excellent clinical descriptions having been ascribed to Hippocrates.[1] However, it is only within recent years that human brucellosis has engaged the interest of clinicians in this country. Thus, in the two states of Iowa and Minnesota, where brucellosis is a serious endemic problem, the first human cases were recognized as recently as 1927. Brucellosis is a disease of major concern at the present time because there are indications that the incidence is on the increase both in domestic animals and in human beings. It has been estimated that the annual cost of this disease to the cattle industry alone in the United States amounts to almost $100,000,000.[2] Although the precise number of cases of human brucellosis is not known, it is most significant that more cases were recognized and reported for the country as a whole during 1947, than during any previous year.[3] It is well then to consider briefly the pathogenesis of human brucellosis with relations to the natural reservoir of the disease; the modes by which human beings contract the disease; the basic tissue reactions following entrance of the microörganisms into the body; means for preventing the disease; and recent advances in treatment.

EPIDEMIOLOGY OF BRUCELLOSIS

It is of fundamental importance to recognize that brucellosis, except under extremely rare conditions, is not transmitted from human to human. *The disease has its reservoir in domestic animals, particularly in cattle, hogs and goats.* Three closely related species of Brucella are the cause of human disease. Figure 1 illustrates certain basic concepts of the epidemiology of brucellosis. *Brucella melitensis,* often considered the most invasive of the three species of Brucella, is found primarily in goats. Because the disease localizes in the udder, the disease is transmitted to man through contact of the skin with contaminated milk, or through the ingestion of milk or milk products. Occasionally, *Br. melitensis* infects cattle. A very serious and disturbing problem relating to this species is based upon the recent findings in Iowa and in Minnesota in that *Br. melitensis* is widely distributed in hogs,

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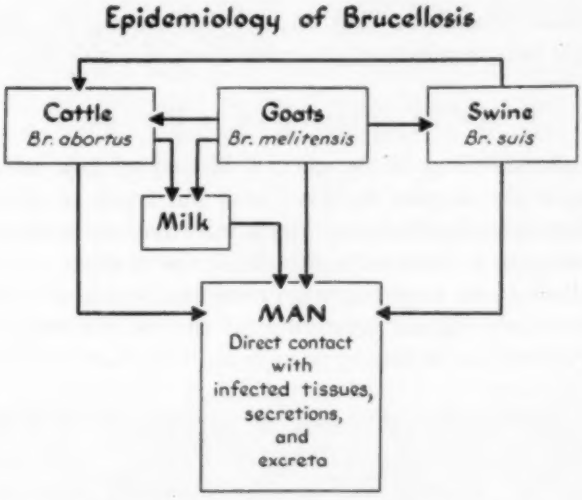


FIG. 1. The epidemiology of brucellosis.

and many human infections due to this species have occurred because of contact with infected porcine tissue.[4, 5] The hog is the natural reservoir for *Br. suis* and man contracts the disease through contact of the skin or mucous membranes with infected tissues or fluids from this animal. However, *Br. suis* also invades dairy cattle, and up until recently, the only serious known epidemics of human brucellosis due to cow's milk were traced to *Br. suis* infections in cattle.[6, 7, 8] *Brucella abortus,* frequently regarded as the least invasive of the species, localizes in the udder of cattle, and in the pregnant uterus of heifers. These features of bovine brucellosis account for human infections caused by drinking raw milk, and by contact with aborted material, uterine discharges and contaminated premises. Human infections due to *Br. abortus* are not always benign, as one is led to believe from a review of the literature. The disease, not infrequently, is severe, and fatal infections have been encountered at the University of Minnesota Hospitals. In most instances, *Br. abortus* causes sporadic infections, but it is highly significant that a major epidemic was recently described as being due to this species.[9] During the Christmas holidays of 1944, an epidemic of 28 human cases occurred in a small community in eastern Maryland. The outbreak was traced to a dairy which supplied raw milk to the community from an infected herd of cattle.

Briefly, then, man contracts brucellosis from infected domestic animals through two principal ways. One mode of infection is through the consumption of raw milk obtained from diseased animals, and also from milk products such as cheese produced from unpasteurized milk. A second avenue of infection is through contact of the skin with tissues, secretions, and excretions of animals with brucellosis. Occasionally, individuals become infected working in the laboratories with cultures of Brucella. There is

some evidence that brucellosis may be included among the air-borne infections, and disease may result from the inhalation of viable Brucella.

Tissue Reactions Due to Brucella

A proper understanding of the natural history of any infectious disease is dependent upon the organs involved and the types of cellular reactions that the invading microbes induce. Such information is often of considerable aid in developing a therapeutic attack on the disease. Early investigations on the pathology of experimental or human brucellosis emphasized the constancy with which organs belonging to the reticulo-endothelial system were invaded by Brucella, including the spleen, liver, bone marrow and lymph nodes. A second feature of the histopathology of brucellosis that has been stressed is the intracellular parasitism of parenchymal cells by the microorganisms. The classical observations of Fabyan [10] revealed this intracellular invasion by Brucella in the experimentally infected guinea pig. Theobald Smith [11] called attention to "the localization and multiplication of bacteria within cells not having phagocytic function" and stated that this unchecked multiplication had a considerable advantage over the host. More recently, others have emphasized the intracellular proliferation of Brucella in the pathogenesis of the disease.[12, 13, 14] The application of these observations to human brucellosis has been bridged by Meyer,[15] who studied the tissues of a young man dying within the first three weeks of a fulminating infection. Massive infiltration of renal epithelial cells by *Br. suis* was demonstrated. Meyer stated "this selective intracellular parasitism in

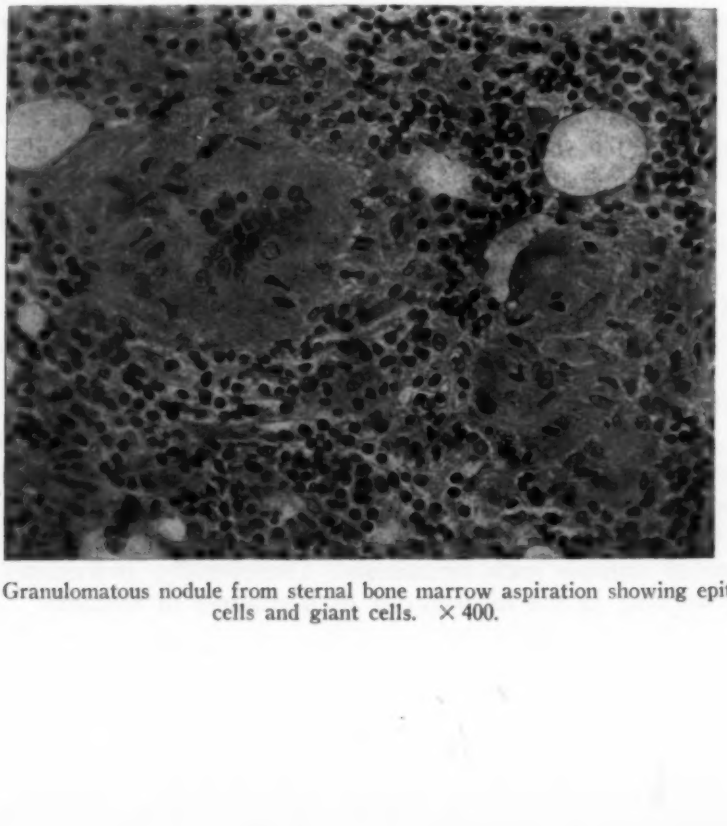


Fig. 2. Granulomatous nodule from sternal bone marrow aspiration showing epithelioid cells and giant cells. × 400.

mesenchyme cells of various organs is doubtless of greatest significance in the pathogenesis of Brucella infections."

My associates and I have been interested in the pathogenesis of brucellosis with particular reference to the histopathology of the tissue reactions. Dr. A. I. Braude has demonstrated in the tissues of the guinea pig the intracellular invasion of hepatic cells by *Br. abortus* within one week after infection. This is confirmatory evidence that Brucella parasitize the so-called nonphagocytic tissue cells. Further studies have been carried out in our clinic to determine the type of reaction that occurs in human tissues as a result of brucellosis, especially in living subjects. Specimens of sternal bone marrow, lymph nodes and liver have been obtained from ambulatory patients by means of biopsy technics. The response of these tissues to invasion by

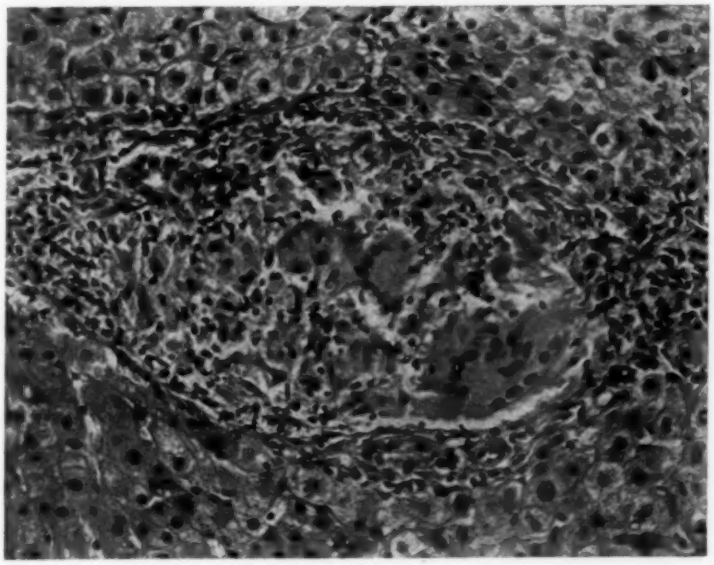


FIG. 3. Granulomatous lesion from human liver showing epithelioid cells and giant cells. × 100.

Brucella has followed a constant type of cellular pattern. The outstanding feature is a proliferation of epithelioid cells, with or without the presence of giant cells of the Langhans and foreign body types, and the presence of lymphocytes, plasma cells, and occasionally, eosinophiles. Necrosis has not been a prominent feature. This type of tissue reaction is not specific for brucellosis and simulates that found in sarcoidosis and tuberculosis. The histopathology of the bone marrow in brucellosis has been reviewed in detail elsewhere with Dr. Dorothy Sundberg.[16] Figure 2 illustrates a nodule found in the marrow of a patient with brucellosis. Localization of Brucella in the sternal marrow may be of considerable aid in the diagnosis of brucellosis. Besides the tissue reactions which the organisms induce, cultures of marrow may yield Brucella when simultaneous blood cultures remain sterile.

Brucella have now been cultured from the sternal marrow in three patients in our clinic when repeated cultures of blood showed no growth of organisms.

Biopsies of the liver have been performed in a group of patients with brucellosis proved bacteriologically. These studies have been made with Dr. F. W. Hoffbauer and Dr. W. W. Walker, and it is significant that in every patient having active brucellosis, hepatic lesions have been seen in sectioned biopsy material. Two types of lesions have been encountered. The first is a periportal infiltration with lymphocytes and plasma cells, and occasional necrotic hepatic cells surrounded by mononuclear cells. The second type of lesion is similar to that which has been described for the bone marrow, and consists of epithelioid cells replacing the hepatic cells with occasional giant cells. Figure 3 represents a specimen of liver from a patient with chronic

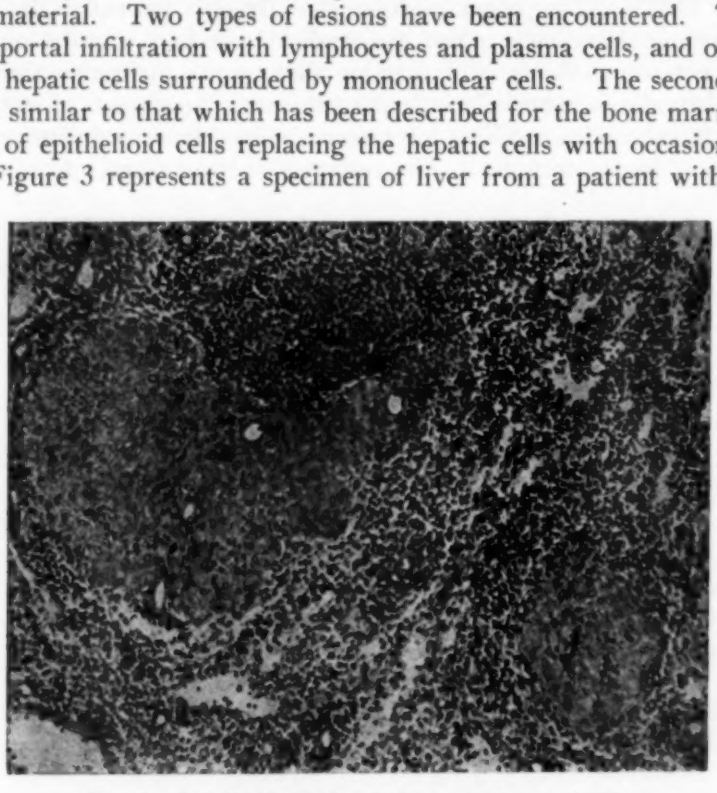


FIG. 4. Sarcoid-like lesion in human spleen. × 175.

brucellosis and shows a nodule comprised of epithelioid cells surrounded by a zone of lymphocytes. It has been stated that the most common visceral lesion occurring in brucellosis involves the liver.[17] On the basis of our own investigations thus far, we are inclined to believe these hepatic changes occur with such frequency in brucellosis that they cannot be considered as a complication, but rather, as a part of the natural history of the disease. Others have considered that brucellosis is at least a contributing factor in the genesis of cirrhosis of the liver.[18, 19, 20, 21] More and more evidence is accumulating in our clinic which would indicate that brucellosis not infrequently may be a contributing cause to serious, and even fatal, human cirrhosis of the liver.

In pursuing the study of the histopathology of brucellosis other tissues have been examined. Figure 4 illustrates a sarcoid-like lesion found in the

spleen of a patient who had a splenectomy carried out during the chronic phase of her illness. This procedure was without benefit to the patient. Figure 5 represents the same kind of a proliferation of epithelioid cells demonstrated in the excised lymph node of another patient.

Investigations conducted by Dr. A. I. Braude in our group in experimentally infected animals have also shown quite clearly that invasion of parenchymal tissue cells by Brucella is followed shortly by the appearance of nodular lesions comprised of epithelioid cells, giant cells and peripheral cellular aggregates of lymphocytes, plasma cells, and an occasional eosinophile cell. While hypersensitivity to Brucella antigen is a common feature of brucellosis, his observations reveal that this phenomenon is not essential

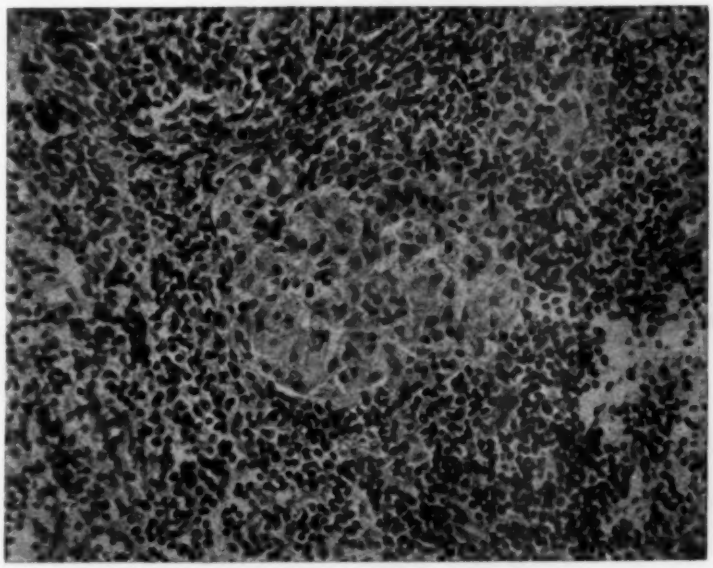


FIG. 5. Granulomatous lesion with epithelioid cells from human lymph node. × 225.

to the genesis of the granulomatous lesions of this disease. However, hypersensitivity of the tissues to some antigen or antigens of the bacterial cell appear to accelerate the formation of these lesions. It would appear that both in experimentally infected animals and in human brucellosis, the response on the part of the tissues with a proliferation of epithelioid cells without accompanying necrosis or caseation represents a desirable and efficient defense mechanism of the host against the invasion of the body by Brucella.

In addition to the foregoing granulomatous lesions in the various viscera, other more demonstrable complications of brucellosis have been observed. Prominent among these have been osseous changes involving the vertebrae, and the pelvic and long bones. It is becoming more and more apparent that osteolytic lesions of the spine may induce a symptom-complex of a herniated

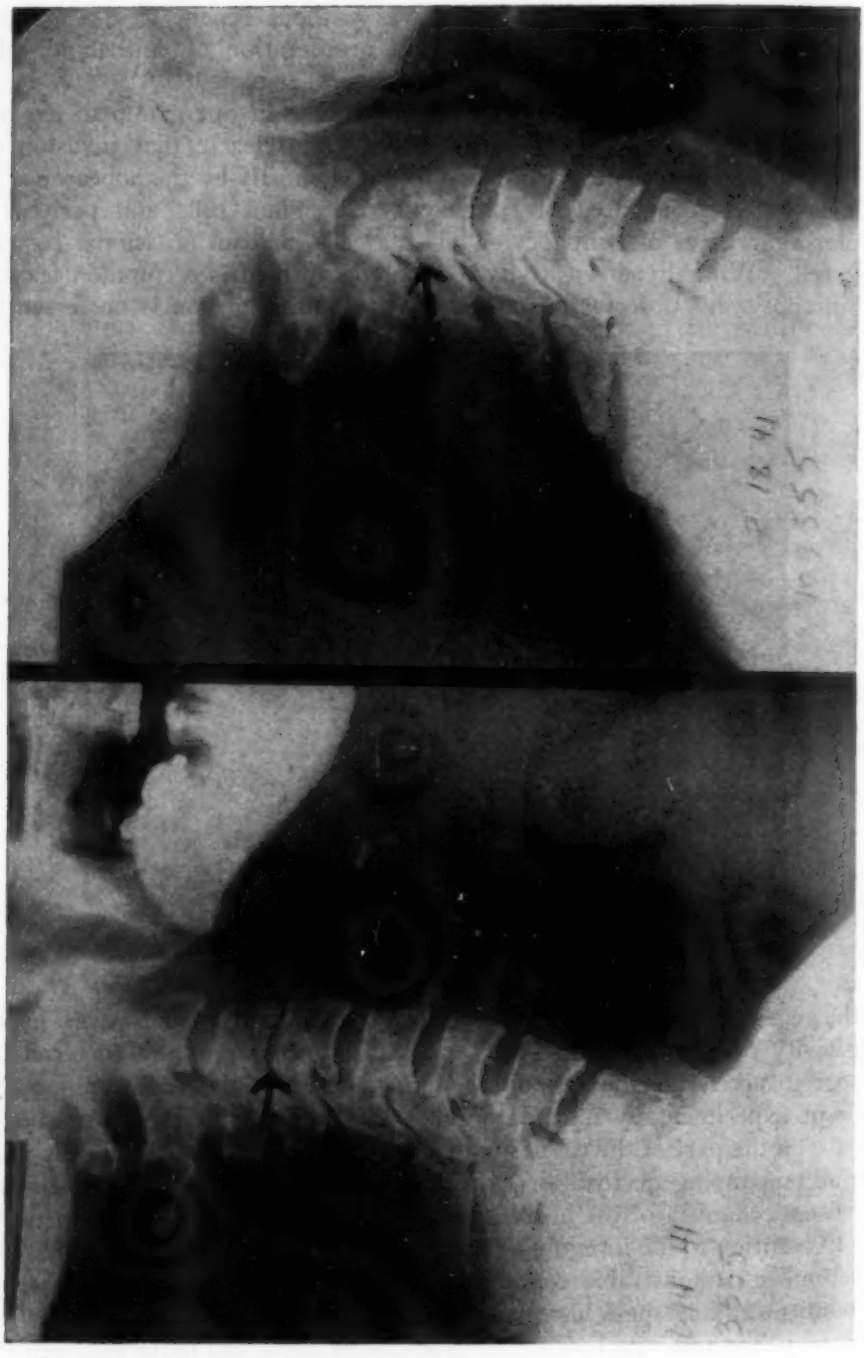


FIG. 6. Acute osteolytic Brucella lesion of cervical spine. X-ray film on right showing new bone formation taken one month after one on left.

intervertebral disc, spondylitis, or distribution of pain over the course of the sciatic nerve. In several instances, a destructive process of the intervertebral disc and adjacent vertebrae has been elicited roentgenologically. Figure 6 illustrates a destructive process in the cervical spine with repair taking place. It is of interest that those who have had extensive experience with infections due to *Br. melitensis* remark upon the infrequent occurrence of bone pathology due to this species.[22, 23] Similarly, osseous lesions do not appear to be too commonly associated with *Br. suis* infections, though by no means are they rare.[24] On the other hand, experience with cases of brucellosis in Minnesota over a period of ten years, which have been due mostly to *Br. abortus*, indicates that osseous pathology is a fairly frequent complication. This is in accord with observations in Uruguay where there is a predominance of brucellosis due to *Br. abortus*.[25] It should be emphasized that during the acute phase of brucellosis periarticular distress is frequently seen, but we have never encountered a single case of chronic arthritis which has resulted from brucellosis.

Another complication of brucellosis, which has been noted in our series of cases, is subacute bacterial endocarditis.[26, 27] Four cases due to *Br. abortus* have been studied and treated. Three of these patients had a fatal illness, but one of them has recovered and remained well for over a year following combined treatment with streptomycin and sulfadiazine.[28] Other less frequently observed complications have included encephalo-meningitis with recovery of *Br. abortus* from the cerebrospinal fluid in two cases; and a pericholecystic abscess due to *Br. suis*. Since symptoms in brucellosis are so commonly referable to the central nervous system, the cerebrospinal fluid should be studied and cultured more often, especially in the chronic cases. In our series of cases, two of our patients having chronic brucellosis with mental depression have committed suicide. Orchitis or epididymitis in the male has not been seen in our series; nor has abortion in the female occurred as a result of brucellosis.

Immune Reactions Due to Brucella

No attempt toward clarifying the pathogenesis of brucellosis would be complete without some discussion of the immune reactions that have been described. While much has been written and ably summarized, particularly by Huddleson,[29] on immunity in brucellosis, not a little confusion accompanies this aspect of the disease. One of the most outstanding features of human brucellosis is the consistency with which hypersensitivity develops following invasion of the tissues by Brucella. In fact, it is difficult to escape the conclusion that the symptomatology of brucellosis is due, in part at least, to a marked sensitivity of the tissues to a Brucella antigen or antigens. This sensitivity is most frequently demonstrated by intradermal tests with appropriate antigens, and very often following such a procedure the patient's symptomatology may be accentuated. The demonstration of dermal sen-

Fig. 6. Acute osteolytic Brucella lesion of cervical spine. X-ray film on right showing new bone formation taken one month after one on left.

sitivity with or without systemic manifestations is oftentimes the basis for employing Brucella antigens for therapeutic purposes. Although it may not be illogical to subject patients with chronic brucellosis to increasing doses of Brucella antigens in attempts to "desensitize" their tissues, our own efforts in the therapy of brucellosis have been toward eradicating viable Brucella from the tissues, thus ridding the body of the source of antigenic material.

Another perplexing aspect of brucellosis is related to the question of natural and acquired immunity to the disease. It has been known for years that immature animals, such as young calves and young goats, are much more resistant to brucellosis than more mature animals, particularly pregnant cattle or goats. In lower animals, Brucella appear to have a predilection for embryonic tissues, mammary glands and for the pregnant uterus. Young children also appear to have a greater resistance to brucellosis than adults, although the former are repeatedly exposed to infective raw milk. Immune studies carried out in this clinic and elsewhere indicate that the tissues of rural children are invaded by Brucella, and mild infections are apparent in some cases, but the incidence of recognized brucellosis in any endemic area is much less under 12 years of age than in older age groups. Studies in progress in this clinic among rural families signify that some adults may also have a relative degree of natural resistance to the disease. On several occasions, it has been observed among closely knit groups exposed to the disease that only one or two individuals may develop acute brucellosis, although immunological studies indicate the remaining persons have been infected. Accurate information is not available as to whether an attack of brucellosis will protect an individual against subsequent exposure. Clinically, it is difficult to determine whether repeated attacks of brucellosis are due to a relapse of the initial disease or are due to a new infection. It would appear from observations made in this clinic on packing plant employees that repeated attacks of brucellosis do occur, and not infrequently, indicating that the immunity which does result from a single infection is only relative. It has now been clearly established that the injection of a viable strain of *Br. abortus* of low virulence into calves will offer a partial protection against subsequent exposure to Bang's disease. For obvious reasons, nothing is known about the protection that the injection of living Brucella might afford human beings. It has been fairly well decided that available preparations of killed Brucella do not provoke acquired immunity to the disease. It is apparent that more information is needed relative to the problems of natural and acquired brucellosis in human beings.

Although much has been written about the humoral immune reactions in brucellosis, their precise significance has often given rise to doubts because of unjustifiable interpretations placed upon them. The response to invasion of the tissues by Brucella that may be studied in the blood include opsonins, complement fixing antibodies and agglutinins. The most widely employed laboratory procedure for diagnostic purposes is the agglutination

reaction. It is now recognized that the appearance of agglutinins in the serum in a titer of 1 to 100 and above has considerable diagnostic significance. On the other hand, these agglutinins may not necessarily be specific for Brucella, since cross reactions occur with *P. tularense,* and Eisele and his group [30] have emphasized that immunization with cholera vaccine will result in a high titer of agglutinins for Brucella. Dr. W. H. Hall has demonstrated the presence of bactericidins against Brucella in the serum of normal individuals, that is, the undiluted and fresh serum will kill appreciable numbers of Brucella. In studying this phenomenon further, he has observed that fresh, undiluted serum from patients with the more chronic form of brucellosis uniformly exhibit a lack of killing power for Brucella. However, when the serum is diluted out, a prozone of killing action is found to be present. The significance of this prozone activity is still being investigated.

Briefly, then, the immunological aspects of brucellosis require further study and elucidation. Although certain serological reactions are of considerable aid in the diagnosis of active brucellosis, their limitations are too frequently overlooked. The nature and significance of hypersensitivity in the genesis of the symptom-complex of brucellosis also merits more attention.

Treatment of Brucellosis

Effective therapy in human brucellosis calls for the administration of an agent or agents which will not only control the infection but which will eradicate Brucella from the body. In a previous communication, it was pointed out that the combined use of streptomycin and sulfadiazine gave more satisfactory therapeutic results than had been previously obtained at the University of Minnesota Hospitals over a period of 10 years.[26] The antibrucella effect of these two compounds was readily evaluated in the fertilized chicken egg.[31, 32] A continuation of these studies has revealed that the action of the combination of streptomycin and sulfadiazine is synergistic, and not merely additive.[33] To date, a number of other compounds in combination with streptomycin have been screened in infected embryos, and streptomycin and sulfadiazine still remain the most desirable ones for human purposes. It should be emphasized that in the infected fertilized hen's egg, the combination is effective against all three species of Brucella, namely, *Br. abortus, Br. suis,* and *Br. melitensis.*

To date, 17 patients with brucellosis have been treated with streptomycin and the sulfonamides, particularly with sulfadiazine. This group includes nine patients for whom the results of therapy were presented in a previous report.[28] These patients are again included in order to provide data on a longer follow-up period after the completion of therapy, which are so essential in the evaluation of treatment in brucellosis. For comparative purposes, the same numbers are given to the patients as those appearing in the first

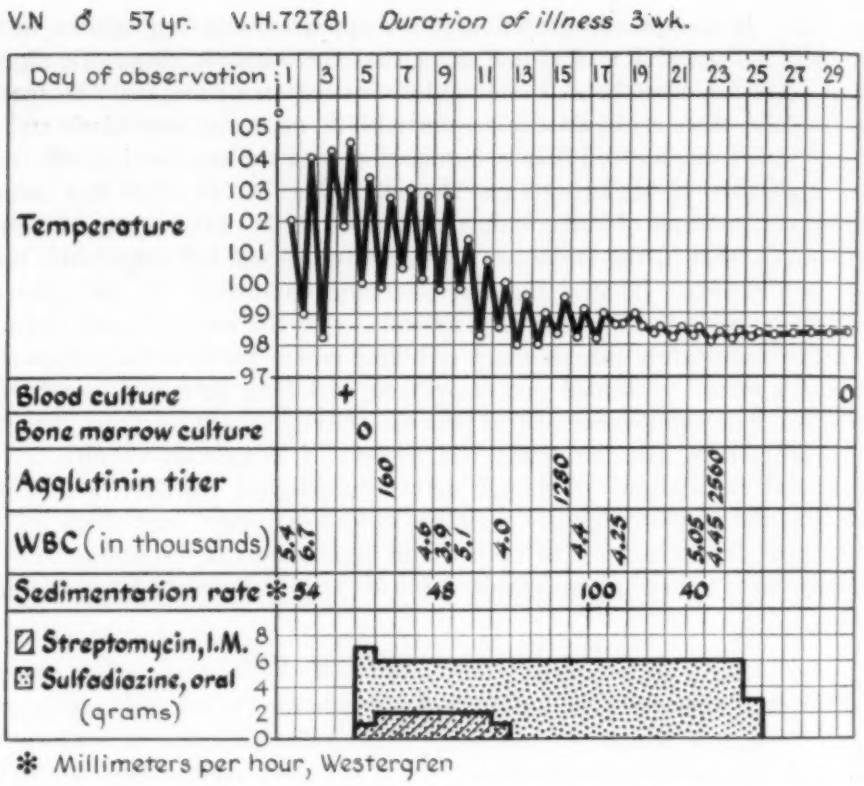

V.N ♂ 57 yr. V.H.72781 Duration of illness 3 wk.
Day of observation 1 3 5 7 9 11 13 15 17 19 21 23 25 27 29
Temperature
105 104 103 102 101 100 99 98 97
Blood culture
Bone marrow culture
Agglutinin titer
160 1280 2560
WBC (in thousands)
5.7 6.7 4.6 3.9 5.1 4.0 4.4 4.25 5.05 4.45
Sedimentation rate * 54 48 100 40
Streptomycin, I.M.
Sulfadiazine, oral
(grams)
8 6 4 2 0
* Millimeters per hour, Westergren

FIG. 7. Illustrating clinical course of patient with acute brucellosis treated with combination of streptomycin and sulfadiazine.

report on therapy. Pertinent data relating to the 17 patients are given in table 1. *Br. abortus* was isolated from 14 of the 17 patients. While organisms were not obtained in the cultures from the remaining three individuals, there was sufficient clinical and serological evidence to permit a diagnosis of active brucellosis. It has been approximately one year since the first patient was treated simultaneously with streptomycin and sulfadiazine at the University Hospitals. During this time, attempts have been made to answer several questions relative to this type of therapy. These have included the following: does the combination of streptomycin and sulfadiazine shorten the clinical course of acute brucellosis? Is the combination effective in chronic cases? Is such therapy of value in either acute or chronic cases when complications are in evidence? What is the optimum schedule of doses for each of the drugs? What toxic complications may one anticipate? How frequently will patients relapse following treatment? Is the development of streptomycin resistant strains of Brucella going to be a problem in therapy? It would appear that experience with 17 patients over a period of one year would provide at least a partial answer to the foregoing questions.

Effect of Streptomycin and Sulfadiazine on the Clinical Course of Acute Brucellosis. An arbitrary division of the patients into acute and chronic cases has been made by designating the acute form as an illness of less than three months in duration. Accordingly, nine of the patients had acute brucellosis, and *Br. abortus* was isolated from all the cases except case 41. It would be expected that the most favorable results would be obtained with the acute cases. Brucellosis is a disease with a variable clinical course. There may be a complete remission of the disease in an acutely ill patient

TABLE I

Summary as of April 1, 1948 of 17 Patients with Brucellosis Treated Simultaneously with Streptomycin and Sulfadiazine

Case No.	Age	Sex	Duration of Disease	Complications	Bacteriology	Treatment and Date of Completion	Comment
27	45	M	9 mos.	Subacute bacterial endocarditis	*Br. abortus* from blood 4 times	Streptomycin—52 gm. in 14 days; sulfadiazine—129 gm. in 22 days. Completed April 24, 1947.	Vertigo from streptomycin persists. Otherwise complete recovery and well for one year.
28	28	F	9 mos.	Radiculoneuritis left arm	*Br. abortus* from blood once; bone marrow once	Streptomycin—57 gm. in 15 days; sulfadiazine—120 gm. in 22 days. Completed April 18, 1947.	Complete recovery. No relapse one year after treatment.
29	28	M	2 mos.	Mesenteric adenitis with disabling right lower quadrant pain	*Br. abortus* from blood once	Streptomycin—22 gm. in 8 days; sulfadiazine—115 gm. in 20 days. Completed Aug. 4, 1947.	Complete recovery. No relapse 8 mos. after treatment.
30	32	M	9 mos.	Spondylitis and radiculitis	*Br. abortus* from blood once	Streptomycin—14.5 gm. in 8 days; sulfadiazine—142 gm. in 24 days. Completed Aug. 7, 1947.	Complete recovery. No relapse 7 mos. after treatment.
31	57	M	3 wk.	None	*Br. abortus* from blood once	Streptomycin—14 gm. in 8 days; sulfadiazine—124 gm. in 21 days. Completed April 28, 1947.	Complete recovery. No relapse in 11 mos.
32	25	M	2 mos.	None	*Br. abortus* from blood twice	Streptomycin—14 gm. in 7 days; sulfadiazine—76 gm. in 12 days. Completed Sept. 11, 1947.	Complete recovery—although spleen palpable at completion of treatment. No relapse in 6 mos.
33	31	F	2 mos.	Old mitral stenosis on rheumatic basis	*Br. abortus* from blood twice	Streptomycin—14 gm. in 7 days; sulfadiazine—102 gm. in 21 days. Completed Oct. 10, 1947.	Complete recovery. No relapse in 5 mos.
34	21	M	1 mo.	None	*Br. abortus* from blood 12 times	4 courses of therapy—1. Streptomycin—16.5 gm. in 9 days; sulfadiazine—66 gm. in 9 days. 2. Streptomycin—8 gm. in 4 days; sulfadiazine—20 gm. in 4 days. 3. Streptomycin—14 gm. in 7 days; sulfadiazine—62 gm. in 13 days. 4. Streptomycin—43.5 gm. in 15 days; sulfadiazine—87 gm. in 15 days. Total streptomycin 82 gm. in 35 days; sulfadiazine 235 gm. in 41 days. Completed Feb. 9, 1948.	Bacteriologic and clinical relapse after first 3 courses. No further relapse 2 mo. after fourth course. No change in in vitro resistance of *Br. abortus* isolated from blood to streptomycin after 3 courses of treatment.

TABLE I—*Continued*

Case No.	Age	Sex	Duration of Disease	Complications	Bacteriology	Treatment and Date of Completion	Comment
35	33	M	1 mo.	Femoral vein phlebothrombosis; pulmonary emboli with infarction; pulmonary effusion; pulmonary edema; lung abscesses; empyema; amebiasis	*Br. abortus* from blood twice	Streptomycin—77 gm. in 28 days; sulfadiazine—181 gm. in 25 days. Completed Sept. 24, 1947. Subsequently received streptomycin, sulfadiazine, penicillin, oxygen, and anticoagulants because of pulmonary suppuration secondary to pulmonary emboli.	18 blood cultures neg. for Brucella following treatment. Seriously ill with pulmonary suppuration not directly related to brucellosis. Recovering slowly.
36	25	M	1 week	None	*Br. abortus* from blood once	Streptomycin—19 gm. in 11 days; sulfadiazine—74 gm. in 13 days. Completed Oct. 27, 1947.	Complete recovery. No relapse in 5 mos.
37	60	M	3 mos.	None	*Br. abortus* from blood 5 times	Streptomycin—18 gm. in 9 days; sulfadiazine—132 gm. in 22 days. Completed Dec. 1, 1947.	Day after treatment completed *Br. abortus* from blood. 9 days after treatment, blood sterile. Feels well with no relapse in 4 mos.
38	31	M	4 mos.	None	*Br. abortus* from blood 4 times	Streptomycin—14.5 gm. in 7½ days; sulfadiazine—138 gm. in 24 days. Completed Dec. 31, 1947.	Complete recovery. No relapse in 3 mos.
39	32	M	9 mos.	Bone destruction rt. sacroiliac region	*Br. abortus* from bone marrow once	Streptomycin—28.5 gm. in 14 days; triple sulfonamide—130 gm. in 35 days. February 16, 1948.	Also bed rest for 3 weeks with extension of rt. leg. Marked improvement. Able to walk. No relapse in 7 weeks.
40	54	M	6 weeks	None	*Br. abortus* from bone marrow once	Streptomycin—30.8 gm. in 15 days; sulfadiazine—44.8 gm. in 15 days. Completed March 6, 1948.	Complete recovery. No relapse in 1 mo.
41	44	M	6 weeks	None	Blood culture sterile 8 times. Bone marrow sterile. Aggls. for *Br. abortus* 1:320	Streptomycin—14.5 gm. in 8 days; sulfadiazine—66 gm. in 14 days. Completed Aug. 25, 1947.	Sulfonamide discontinued because of drug fever and dermatitis. Complete recovery. No relapse in 7 mos.
42	40	M	13 mos.	None	Blood culture sterile 3 times. Bone marrow sterile. Aggls. for *Br. abortus* 1:320	Streptomycin—12 gm. in 7 days; triple sulfonamide—76 gm. in 19 days. Completed Jan. 16, 1948.	Complete recovery. No relapse in 2½ mos.
43	52	M	2 yr.	None	Blood culture sterile 2 times. Bone marrow sterile. Aggls. for *Br. abortus* 1:320	Streptomycin—14 gm. in 8 days; triple sulfonamide—68 gm. in 19 days. Completed Dec. 24, 1947.	Slight improvement. Weakness and sweats continued.

following a period of bed rest. For this reason, it is not too easy to interpret the results of therapy in case 31, whose clinical course is illustrated in figure 7. This individual had been ill for three weeks and after receiving streptomycin for eight days, and sulfadiazine for a total of 21 days, he recovered completely and has not had a relapse for 11 months. Because the patient became afebrile and abacteremic coincident with therapy, and has remained in good health for almost a year, it is believed that specific treatment in this instance did benefit the patient.

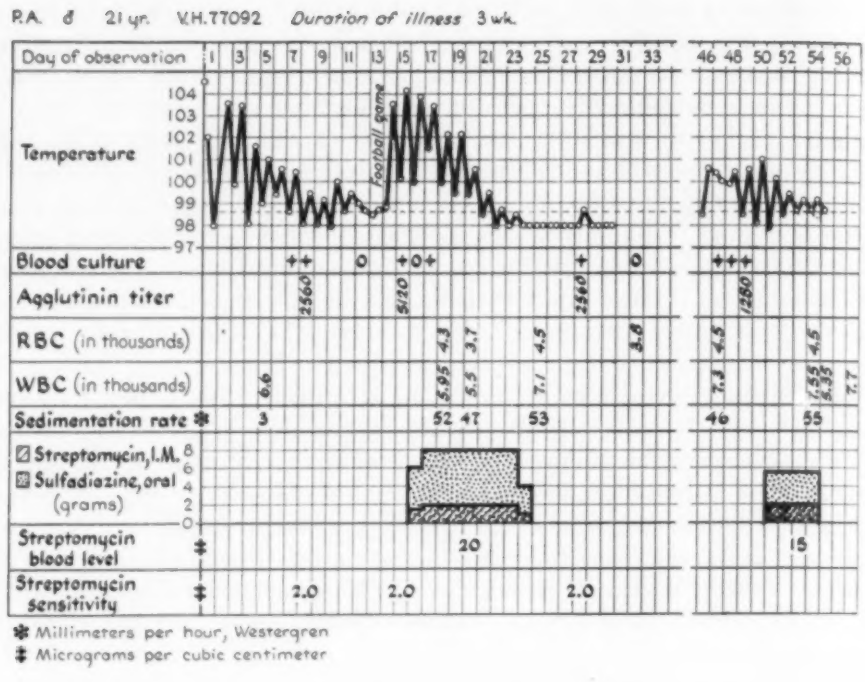
On the other hand, case 34 was a young individual who had been acutely ill for only one month. Although he had had adequate rest in bed, several courses of streptomycin and sulfadiazine were required before his illness appeared to be terminated. His course is presented in figure 8. In some respects, his illness simulated that observed in malaria. It is to be noted that following rest in bed his temperature declined and he felt so well that he prevailed upon the staff to permit him to attend a night football game. A few hours out in the brisk, open air was sufficient to precipitate a relapse of his brucellosis. In an attempt to evaluate a short course of streptomycin and sulfadiazine he was given both these drugs at the same time for only nine days. Shortly after completing treatment he suffered from another relapse. He was started on a second course but because of a death in his family, and improvement in his condition, treatment was continued for only four days, and he was allowed to attend the funeral. He had another relapse. Following an abbreviated third course of treatment, he had another relapse. But after a more intensive therapeutic schedule, he appears to have recovered. Other remarkable features of this case are that he did not develop any toxic reactions to either streptomycin or sulfadiazine, and the various cultures of *Br. abortus* isolated from his blood subsequent to the initiation of treatment did not reveal any diminution in in vitro sensitivity to streptomycin.

On the basis of observations in this group of nine cases with acute brucellosis, it takes from a week to 10 days of combined treatment before the patients experience definite improvement, and about that length of time before the temperature begins to assume normal values.

Effect of Streptomycin and Sulfadiazine on the Clinical Course of Chronic Brucellosis. Eight patients had an illness of three months or more, thus classifying them as chronic cases. *Br. abortus* was isolated from six of the eight patients. Contrary to expectations, the effect of therapy on the clinical course of this group of patients was similar to that obtained in the acutely ill patients, though slightly larger amounts of streptomycin were administered to the chronically ill patients.

Before any definite conclusions are formulated it is very apparent that further patients having chronic brucellosis of the type exhibited by cases 42 and 43 will have to be treated. These individuals represent the chronic state of brucellosis without definite localizing findings, and with negative cultural studies. In many instances of chronic brucellosis, the febrile response is absent or low-grade. We have been reluctant up to the present time to evaluate specific therapy in this type of case because in so many instances the precise diagnosis is always in doubt. Furthermore, it is in this type of case where abuses of therapeutic procedures have occurred in the past. We anticipate that streptomycin and sulfadiazine will be employed uncritically and without benefit in doubtful cases of chronic brucellosis.

Effect of Streptomycin and Sulfadiazine on the Complications of Brucellosis. Perhaps the most rigid test for any specific therapeutic procedure in



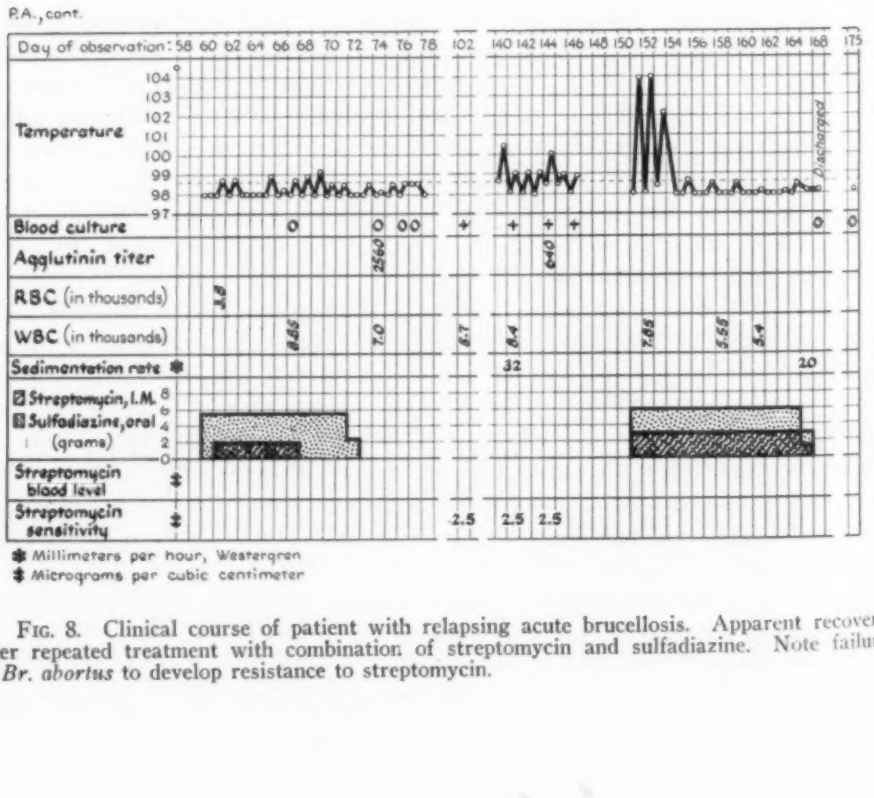


FIG. 8. Clinical course of patient with relapsing acute brucellosis. Apparent recovery after repeated treatment with combination of streptomycin and sulfadiazine. Note failure of *Br. abortus* to develop resistance to streptomycin.

brucellosis relates to the effect on some of the more severe complications. The second patient to receive the combined therapy in our clinic was an individual with subacute bacterial endocarditis due to *Br. abortus*. Experience with this complication in three previous patients had emphasized the futility of all prevailing therapy. Streptomycin and sulfadiazine in case 27 have resulted in a remission that has now lasted for one year. This individual has apparently recovered from a heretofore fatal complication of brucellosis.

Case 28 had been quite ill for nine months spending most of the time in bed. She had only partial use of her left arm because of a radiculoneuritis. This abated shortly after instituting combined treatment and she has remained well for one year.

Case 29 had an unusual type of complication in the form of recurrent and disabling pain in the right lower quadrant. Each attack was associated with fever, weakness, sweats and enlarged peripheral lymph nodes. While the diagnosis of intermittent appendicitis was entertained, it was concluded that there was simultaneous enlargement of the mesenteric lymph nodes along with the peripheral nodes to account for the pain. Following treatment, this patient has been free of pain or symptoms of the disease for eight months.

Infiltration of bone by Brucella may provoke a chronic illness which may be completely disabling as illustrated by cases 30 and 39. Case 30 had spondylitis of the lumbosacral area and an accompanying radiculitis. The pain was so severe that the daily administering of opiates was required. Before treatment was completed, this patient's pain had subsided to such a degree that he was able to rest without the aid of morphine. He recovered completely and has had no relapse in five months. Case 39 had a completely disabling and very painful destructive process of the right sacroiliac joint. Following treatment he was relieved of pain on walking, and within one month was able to work.

Optimum Doses of Streptomycin and Sulfadiazine. The treatment of 17 patients with the two drugs does not permit an unqualified statement as to optimum dose schedules. In the initial report, it was recommended that 0.5 gm. of streptomycin should be given intramuscularly every six hours for one week. At the same time that streptomycin is started, sulfadiazine is administered orally in an initial dose of 3 to 4 gm., and then 1 gm. every four hours for at least three weeks. Additional experience would indicate that the same six-hour dose of streptomycin should be given for two weeks, and sulfadiazine should be administered as stated for a total of three weeks. Whether such a schedule will prove adequate for all cases remains to be evaluated. It is recommended that the total daily dose of streptomycin should not exceed 2 gm. Larger doses may very well induce disagreeable and even disabling toxic reactions. It has been observed in this clinic by Miss Dorothy Anderson that the growth of freshly isolated strains of *Br. abortus* is consistently inhibited by 2 mcgm. of streptomycin or less per milliliter. One hour after injections of 0.5 gm. of streptomycin, serum

levels of 15 to 20 mcgm. are readily obtained. The foregoing doses of sulfadiazine yield levels of 7 to 10 mg. per cubic milliliter.

Thus far, the only toxic complication that has been ascribed to streptomycin occurred in case 27, who had subacute bacterial endocarditis, and who received up to 4 gm. of streptomycin a day for a total of 52 gm. in 14 days. This patient has involvement of the vestibular apparatus so that his equilibrium is disturbed making it difficult for him to carry out some of his duties as a farmer. This disturbance has persisted for a year, with little or no improvement since the onset. It was necessary to discontinue therapy with sulfadiazine in case 41 because of the appearance of fever and a dermatitis. Otherwise, no toxic reactions were related to sulfonamide therapy.

Because both streptomycin and sulfadiazine are drugs which may cause serious toxic complications, it is desirable that patients undergoing therapy should be treated in a hospital under close supervision. These precautions mean that the treatment of brucellosis is not inexpensive. Therefore, it is essential that the physician in attendance should be reasonably sure of his diagnosis.

Relapses Following Treatment with Streptomycin and Sulfadiazine. Since brucellosis is an illness which may subside spontaneously, only to manifest a relapse repeatedly, an evaluation of any specific therapy must take into consideration the incidence of relapses. Case 34 is an example of an acute case of brucellosis which was inadequately treated, and bacteriological and clinical relapses occurred. This case emphasizes the necessity of utilizing combined treatment for at least 14 days. Case 37 represented an instance of chronic brucellosis in which marked improvement occurred coincident with treatment, but immediately following the completion of therapy, a positive blood culture for *Br. abortus* was obtained. However, the patient has continued in a good state of health, and a subsequent culture of blood remained sterile. Case 43, representing a chronic case of brucellosis, manifested little or no improvement. It is possible that he might have benefited with a more prolonged course of treatment, especially with streptomycin. In this series of cases, then, the low relapse rate has been quite encouraging.

Development of Resistance of Brucella to Streptomycin. Microörganisms in general have a remarkable tendency to develop increased resistance to streptomycin as a result of therapy.[34] In a case not included in this series, Hall and Spink[35] observed a patient from whose blood a streptomycin-sensitive strain of *Br. abortus* was obtained. Following a month's therapy with streptomycin, several cultures of blood revealed the presence of a strain of *Br. abortus* which was highly resistant to the in vitro action of streptomycin. It was apparent, then, that resistance to streptomycin could develop as a result of treatment. However, subsequent studies included in this report, have not revealed another instance of such acquired resistance. In two cases, 34 and 37, Brucella were studied in vitro after treatment with streptomycin and there was no diminution of sensitivity of the organisms

to the drug. It is possible that resistance to either streptomycin or sulfadiazine is less likely to develop when both are administered simultaneously.

Prevention of Brucellosis

Human brucellosis will always constitute a problem in clinical medicine as long as the reservoir for the disease persists in domestic animals. As much support as possible should be given to the efforts to eradicate the animal reservoir of the disease. In cattle, no single plan of elimination will be effective under all conditions. The area testing of herds of cattle, with slaughtering of positive reactors, is essential under certain circumstances. Immunization with strain 19 of *Br. abortus* should be encouraged in *young* stock. The extermination of brucellosis in swine is beset with more difficult problems. Wiping out brucellosis in goats should not be too great a problem in this country, mainly because the goat population is concentrated west of the Mississippi in the southwestern states. It is quite clear that the eradication of the animal reservoir of brucellosis will require the combined support of farmers, livestock producers, veterinarians, packing plant authorities and public health officials.

Since it is not unlikely that the animal reservoir of brucellosis will be a threat for some years to come, efforts should be made to prevent the transmission of brucellosis to human beings. It is well established that a significant segment of the general population contracts the disease through drinking unpasteurized cows' milk, ingesting raw cream or cream products, and eating cheese prepared from unpasteurized goats' milk. Therefore, the medical profession should encourage the pasteurization of all animal milk used for human consumption. Strict legislation is essential to accomplish this, and the opposition in some quarters will not be mild. It is appropriate to call attention at this meeting of the American College of Physicians in San Francisco that in 1917 Fleischner and Meyer [36] pointed out that practically all the certified milk in the San Francisco Bay regions contained *Br. abortus*. Thirty years later, Dr. Karl Meyer has stated that all milk used for human consumption should be pasteurized because of the continued menace of brucellosis.[37]

Another segment or segments of the population are being exposed to brucellosis because of their contact with diseased animals. This makes brucellosis an occupational disease for farmers, livestock workers, veterinarians and those working in slaughter houses. It should be admitted that at the present time under these circumstances there are no practical means for protecting susceptible individuals from contracting the disease from infected animals. The solution of this problem ultimately resides in the elimination of brucellosis from the animals. No dependable methods of immunization against brucellosis for man are available.

Summary and Conclusions

1. Human brucellosis is a major problem in public health in some sections of this country. There are indications that the incidence of the disease is on the increase.

2. The reservoir of the disease resides in domestic animals, especially cattle, swine and goats. The disease is transmitted either directly or indirectly to human beings from infected animals, and very rarely, if at all, from human to human.

3. Intracellular parasitism results from the invasion of tissues by Brucella resulting in the characteristic, but not specific, tissue reaction of proliferation of epithelioid cells and giant cells. In addition, complications include destructive osseous lesions, subacute bacterial endocarditis, encephalitis, and grossly suppurative lesions.

4. Hypersensitivity of the tissues to an antigen or antigens of Brucella is a constant feature of brucellosis, and the symptom-complex of the disease may depend, in part at least, upon this state of hypersensitivity.

5. The most satisfactory treatment to date for both acute and chronic cases of brucellosis is a combination of streptomycin and sulfadiazine. Thus far, 17 patients have been treated with a maximum follow-up period of one year. The following conclusions appear justified at the present time: *a*. The clinical course of both acute and chronic brucellosis is shortened by this combined therapy. *b*. The combination is effective against such complications of brucellosis as subacute bacterial endocarditis and spondylitis. *c*. Optimum doses remain to be worked out, but at present it is recommended that 0.5 gm. streptomycin be given intramuscularly every six hours for two weeks. At the same time that therapy with streptomycin is started, 3 to 4 gm. of sulfadiazine should be administered orally, and then 1 gm. every four hours for a total of two weeks. Toxic complications from streptomycin have not been encountered in patients receiving a maximum of 2 gm. per day.* Thus far, streptomycin-resistant strains of Brucella have not been recovered from patients as a result of combined therapy.

6. The ultimate elimination of human brucellosis depends upon eradicating the disease from domestic animals. All efforts along this direction should be vigorously supported by the medical profession. This will take time to accomplish. In the meantime, other preventive means should be demanded such as the compulsory pasteurization of all milk destined for human consumption, and the pasteurization of all milk utilized for the production of butter and cheese.

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* Since this manuscript was submitted for publication an instance of vestibular dysfunction has been encountered in a patient receiving 2 gm. daily for 14 days.

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HOARSENESS IN HEART DISEASE*

By J. Lawn Thompson, Jr., M.D., F.A.C.P., and Albert D. Kistin, M.D., *Washington, D. C.*

Left recurrent laryngeal nerve palsy in association with heart disease is apparently very uncommon. Review of the literature reveals sporadic reports. We have been able to find only 30 cases in which necropsy findings are recorded. Mitral stenosis, coronary arteriosclerotic heart disease with congestive failure, and congenital heart disease with pulmonary artery dilatation are among the etiological factors reported. From a review of the literature and study of the cases herein reported it is apparent that dilatation of the pulmonary artery is the prime cause of the nerve injury. Other common cardiovascular abnormalities causing left recurrent laryngeal nerve palsy (manifested by hoarseness) are aneurysm of the arch of the aorta and aneurysm of the innominate or subclavian arteries. In each of our cases the only complaint at time of hospitalization was that of hoarseness. This is significant, because it brings into focus heart disease as an important consideration in the differential diagnosis of that complaint. Two cases are herein reported, one with autopsy findings and the other with angiocardiographic studies in which the evidence favors the conception that pulmonary artery dilatation is the major mechanism in the compression and subsequent degeneration of the left recurrent laryngeal nerve.

Case Reports

Case 1. M. B. C., age 30, was admitted to the hospital complaining of hoarseness of three weeks' duration. The past history revealed no significant illness except that of asthma for which he had been discharged from the Army two years previously. The physical examination revealed the following significant points: The heart was enlarged downward and to the left, the point of maximal impulse being 15 cm. from the mid-sternal line in the fifth intercostal space; there was a soft diastolic murmur heard in the mitral area with an associated harsh systolic murmur, the latter murmur being transmitted to the base of the left lung posteriorly; there was an aortic diastolic murmur heard best to the left of the sternum in the third intercostal space. The blood pressure in each arm was 100 mm. Hg systolic and 50 diastolic. The lung fields were clear throughout. Laryngoscopic examination revealed flaccid paralysis of the left vocal cord. Roentgen-ray examination revealed an enlarged triangular-shaped heart shadow in the postero-anterior view, while in the right oblique view there was slight posterior displacement of the esophagus and a very prominent pulmonary segment (figure 1). An electrocardiogram done at this time was interpreted as being normal.

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Six months later the patient was readmitted complaining of a cough productive of blood-tinged sputum and of marked shortness of breath. The physical examination revealed essentially the same cardiac findings but there were noted moist râles at the bases of the lungs, bilaterally. There was no evident peripheral edema. The course in the hospital revealed daily temperature elevations to 101°, and the spleen was soon

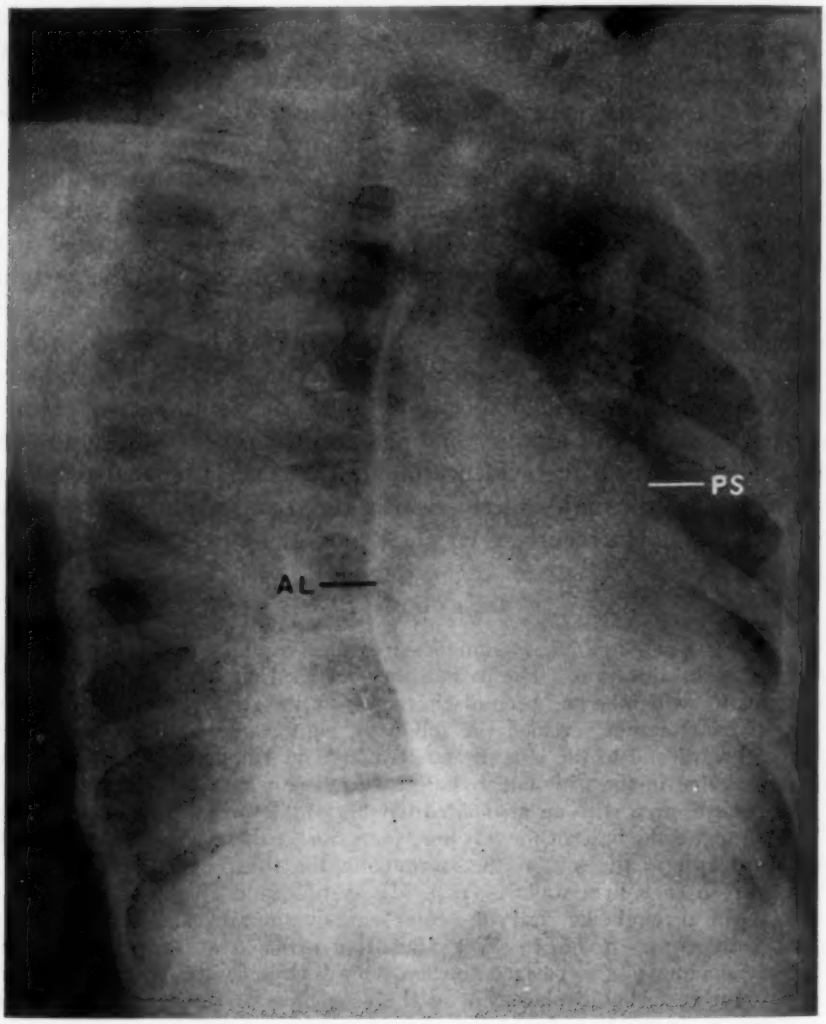

FIG. 1. *Case 1.* Roentgenogram of the chest, right anterior oblique view with barium-filled esophagus. There is slight posterior displacement of the esophagus indicating slight enlargement of the left atrium (AL). The pulmonary segment (PS) is very prominent.

noted to become palpable. Blood cultures were consistently negative, the course was rapidly downward, and death ensued.

Pertinent postmortem findings: The body was well nourished and well developed. There was moderate cyanosis.

Heart: The heart was markedly enlarged. In situ, the upper part of the left border was convex and consisted of pulmonary artery. Most of the anterior surface

FIG. 2. *Case 1.* Photograph of dissection. Anterior view. The left lung has been retracted and the heart has been rotated slightly clockwise as seen from above. For demonstration the flattened, discolored portion of the left recurrent laryngeal nerve has been pulled up from its original location between the arch of the aorta and the left pulmonary artery. A—arch of aorta. I—innominate artery. LCC—left common carotid artery. LS—left subclavian artery. V—vagus nerve. LA—ligamentum arteriosum. PA—pulmonary artery showing dilatation (compare with diameter of arch of aorta). LPA—left pulmonary artery. LPV—left pulmonary vein. AL—left auricle. RV—right ventricle. (a)—site from which section shown in figure 4 was prepared. (b)—flattened, discolored portion of left recurrent laryngeal nerve and site from which section shown in figure 5 was prepared. Note the relations of aortic arch, left pulmonary artery and ligamentum arteriosum to the nerve and the remoteness of the left auricle from the nerve.

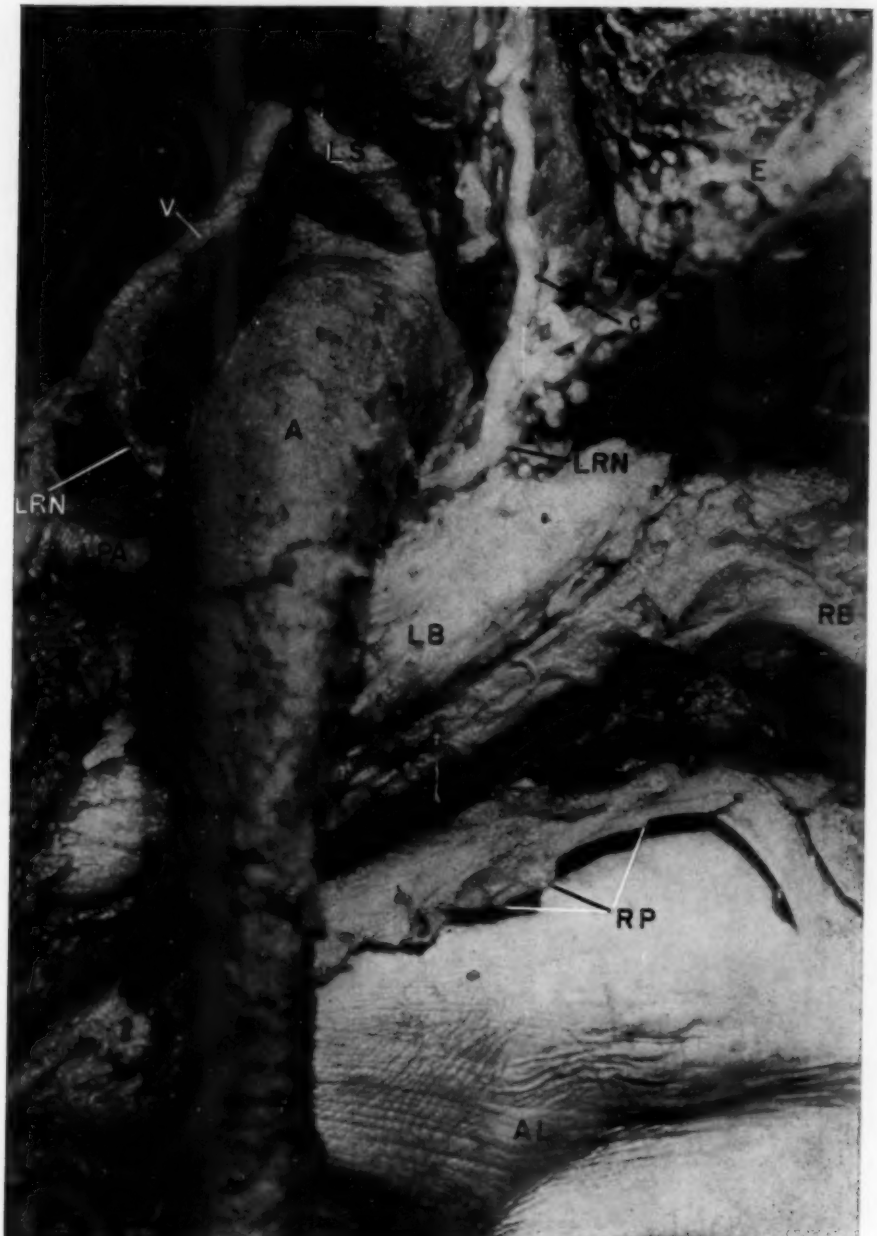

FIG. 3. *Case 1.* Photograph of dissection. Posterior view. A—arch of aorta. LS—left subclavian artery. V—vagus nerve. LRN—left recurrent laryngeal nerve. E—retracted esophagus. LPA—left pulmonary artery. LB—left bronchus. RB—right bronchus. AL—left atrium. RP—cut edge of pericardium. (c)—site from which section shown in figure 6 was prepared. Note the relations of the aortic arch and left pulmonary artery to the nerve and the remoteness of left atrium from the nerve.

was made up of the right ventricle. There was considerable dilatation of both ventricles and some dilatation of the left atrium. The weight of the heart (with 2.5 cm. of the aorta and the pulmonary artery attached) was 530 gm. The left ventricular wall measured 14 mm. and the right ventricular wall measured 6 mm., each measurement being made midway between the base and the apex. There was thickening of the left atrial wall. The valve ring measurements were as follows: tricuspid 120 mm., pulmonary 80 mm., mitral 117 mm., and aortic 60 mm. Over a distance of about 3.5 cm. the anterior leaflet of the mitral valve was considerably thickened and its free edge was thickened, rolled and smooth. The attachments of the chordae tendineae to

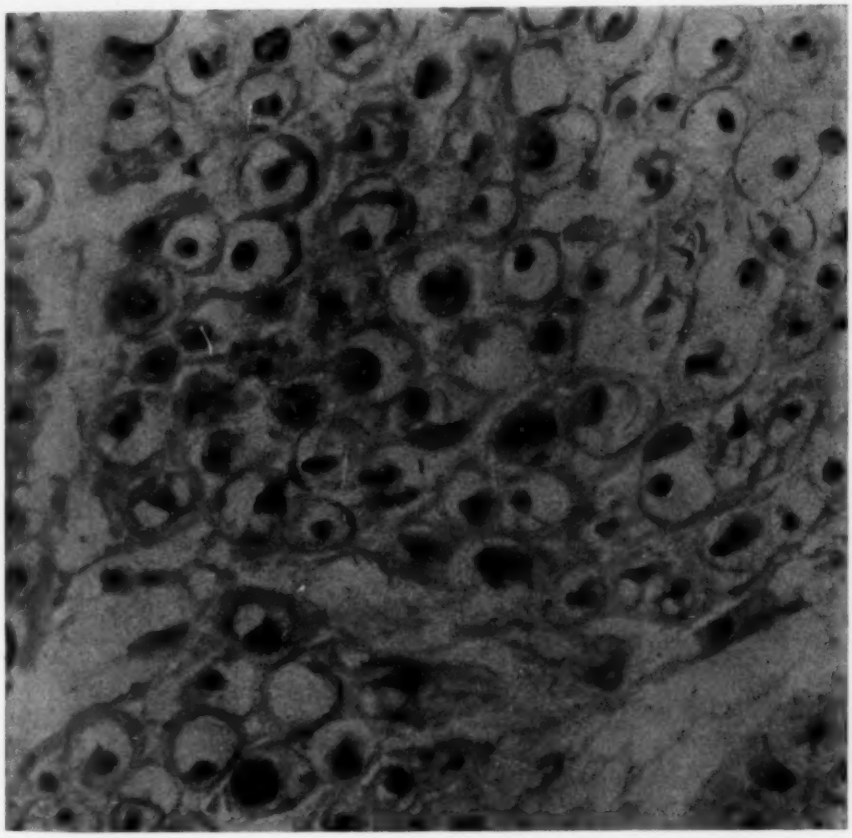

FIG. 4. *Case 1.* Photomicrograph of section of left recurrent laryngeal nerve from the proximal portion near the origin from the vagus (a in figure 2), Bodian's stain for axone cylinders. The axone cylinders are intact.

the mitral valve were thickened, shortened, distorted, nodular and matted together. On the surfaces of the thickened chordae tendineae at their attachments to the valve were very fine, dull, gray-pink nodules. Although the mitral valve was distorted, the degree of stenosis was minimal. The endocardium of the posterior wall of the left atrium, covering an area of about 4 by 5 cm., and directly above the attachment of the posterior cusp of the mitral valve, was dull, mottled gray, rough and traversed by fine, irregular ridges and depressions. The only abnormality noted in any of the coronary arteries was that of slight thickening in the proximal 3 cm. of

the left anterior descending branch. The gross appearance of the myocardium was normal. The pulmonary artery was dilated and there was a yellowish patch noted on the intima at the bifurcation.

Left recurrent laryngeal nerve: The relation of this nerve to the pulmonary artery, aortic arch, and ligamentum arteriosum was carefully determined (figures 2

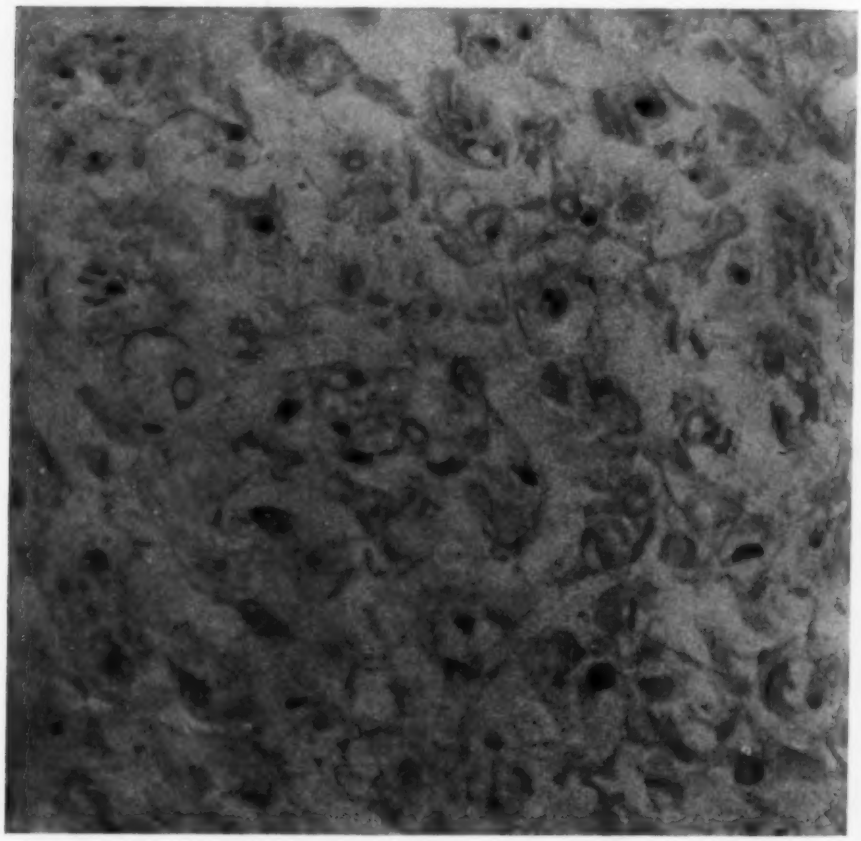

FIG. 5. *Case 1.* Photomicrograph of section of left recurrent laryngeal nerve from the portion lying between the aortic arch and the left pulmonary artery (b in figure 2). Bodian's stain for axone cylinders. There is considerable degeneration of axone cylinders.

and 3). The nerve lay just lateral and in close apposition to the ligamentum arteriosum. The arch of the aorta was immediately superior, and the left pulmonary artery immediately inferior to it. The ligamentum arteriosum was 12 mm. long and 3 mm. wide; it was tough and about the same color and consistency as the adjacent aorta. The uppermost border of the left atrium was a considerable distance below the nerve and was separated from it by the left pulmonary artery and the left bronchus. The portion of the nerve between the left pulmonary artery and the arch of aorta was flattened and showed reddish brown discoloration.

Lungs and pleural cavities: There were approximately 200 c.c. of light brown fluid containing fibrin particles in the right pleural cavity and 300 c.c. of similar fluid in the left pleural cavity. The right lung was firmly adherent posteriorly to the thoracic cage. The external surface was purple-red, and there was no crepitation

anywhere in the lung. The cut surface of the right lung was dark purple-red, firm and moist throughout. The lateral portion of the left lung was firmly attached to the thoracic cage by adhesions. There was no crepitation in the upper lobe but some crepitation in the lower lobe. The cut surface of the left lung was firm and purple-red in the upper lobe and was bright red and wet in the lower lobe.

Microscopic Observations. Heart: A number of characteristic Aschoff bodies were present in the perivascular and interstitial tissues of all chambers and in the atrioventricular bundle. In addition, diffuse infiltrations of cells were present in the

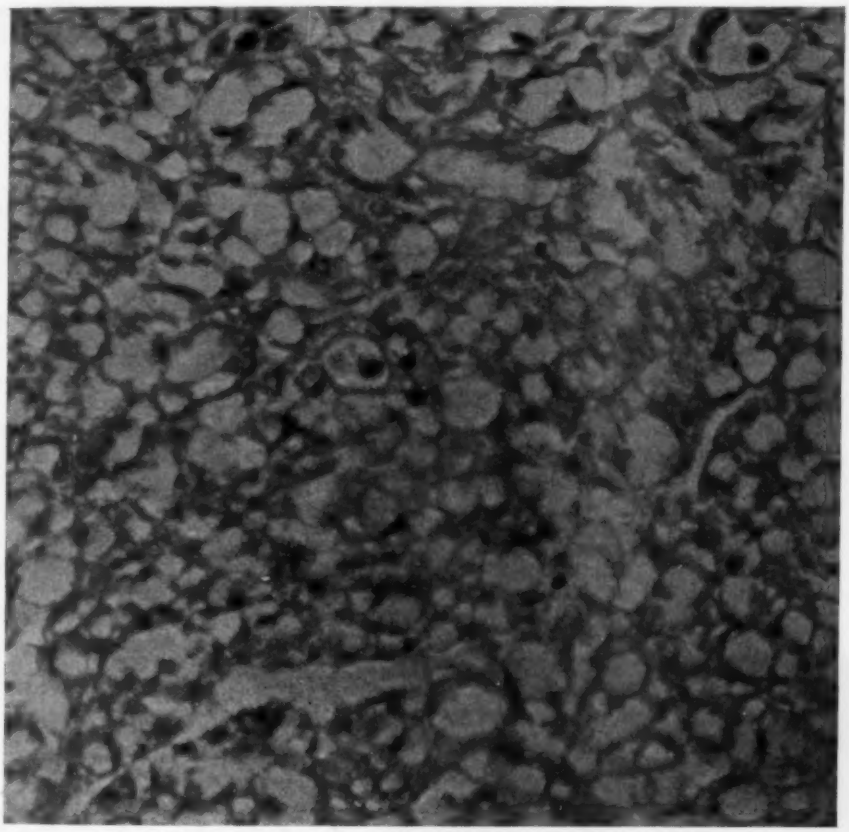

FIG. 6. *Case 1.* Photomicrograph of section of left recurrent laryngeal nerve from a portion of the nerve distal to that lying between aortic arch and left pulmonary artery (c in figure 3). Bodian's stain for axone cylinders. There is considerable degeneration of axone cylinders.

myocardium of all chambers, in the endocardium and epicardium of the left atrium, in the epicardial sheaths of the roots of the aorta and pulmonary artery, in the intima and media of the root of the aorta, in the mitral ring and mitral valve, and in the tricuspid ring and tricuspid valve. These cells were lymphocytes and larger mononuclear cells with irregular pyknotic and vesicular nuclei, some containing prominent nucleoli. In all chambers there were foci of necrosis of the myocardium. The endocardium of the left atrium was considerably thickened and edematous. Sections of the grossly distorted portion of the mitral valve revealed considerable thickening by fibrous connective tissue, edema, and vascularization.

Left recurrent laryngeal nerve: Sections from three levels of the left recurrent laryngeal nerve were prepared: (*a*) the proximal portion at its origin from the vagus, (*b*) the portion of nerve that lay between the left pulmonary artery and aorta, and (*c*) from a portion distal to that which lay between the pulmonary artery and the aorta. All three portions were processed simultaneously by Bodian's method,[1] a piece of normal spinal cord being used as a control. Sections of the control spinal cord revealed intact axones as did sections prepared from level (a) (figure 4). Those prepared from levels (b) and (c) revealed considerable degeneration of axones (figures 5 and 6).

Lungs: Many of the alveolar spaces were filled with red blood cells, a few lymphocytes, and polymorphonuclear leukocytes. In many alveoli there were also a number of macrophages with a great deal of brown granular pigment in the cytoplasm. The alveolar walls were considerably thickened and infiltrated with lymphocytes and large mononuclear cells with large, round and oval vesicular nuclei and distinct nucleoli. The capillaries in some regions were intensely congested. In the right upper lobe there was a sub-pleural accumulation of cells which resembled an Aschoff body. The walls of some of the pulmonary arterioles were considerably thickened, stained diffusely eosinophilic and contained few nuclei.

Anatomic Diagnosis: (1) Rheumatic valvulitis of the mitral valve with fibrosis and deformity; rheumatic valvulitis of the tricuspid valve; rheumatic mural endocarditis of the left atrium; hypertrophy of the myocardium of all chambers; (2) Hemorrhagic and interstitial pneumonitis; fibrous pleuritis of both lungs.

Comment: The clinical and pathological features of the pneumonitis resembled those that have been described in pneumonitis associated with active rheumatic fever. It was believed that the pneumonitis was a manifestation of an acute rheumatic state which precipitated the terminal event in this case.

Case 2. H. F. E., age 31, was admitted to the hospital complaining of hoarseness of three months' duration. The past history revealed that he had been discharged from the military service because of "valvular heart disease." Pertinent physical

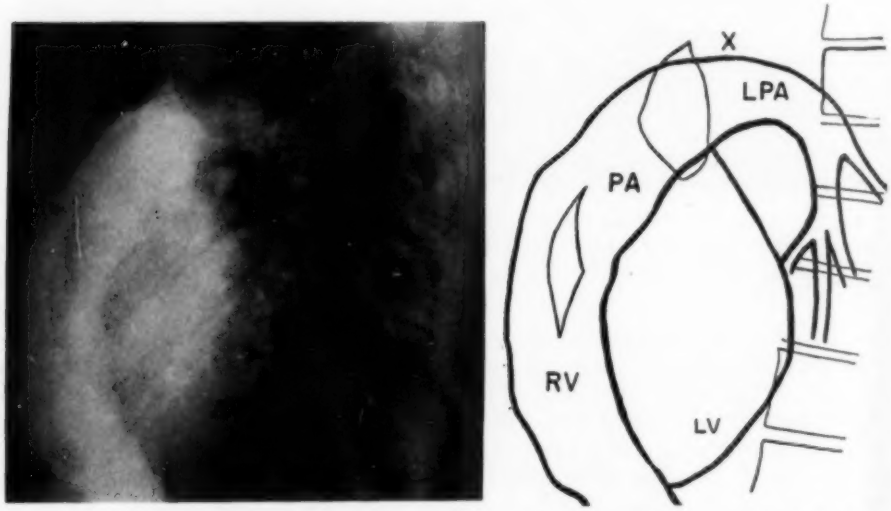

FIG. 7. *Case 2.* Angiocardiogram 3 sec. after injection of 70 per cent diodrast into arm vein. Left oblique view. PA—main stem of pulmonary artery. LPA—left pulmonary artery. RV—right ventricle. LV—left ventricle. The main stem and left branch of the pulmonary artery are dilated. The right ventricle is elongated. X—approximate location of left recurrent laryngeal nerve.

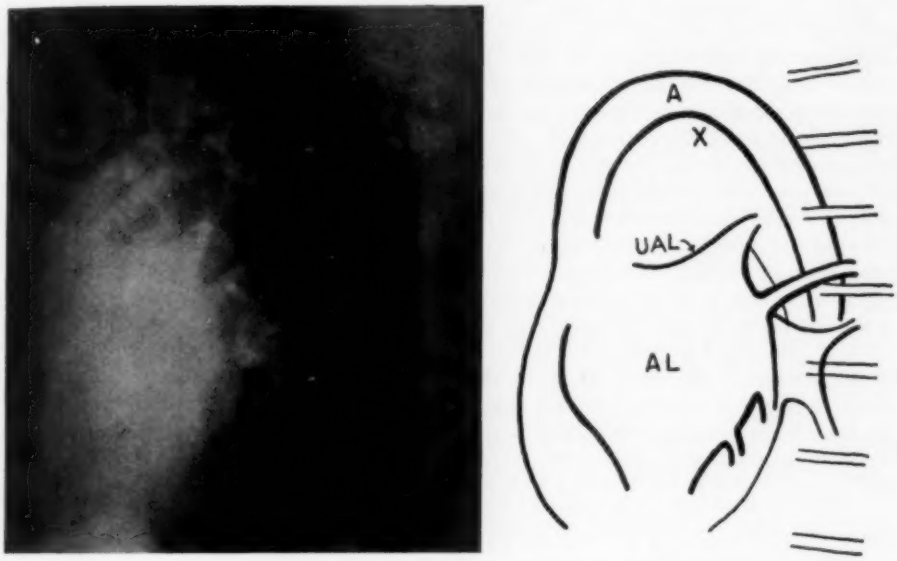

FIG. 8. *Case 2.* Angiocardiogram 11 sec. after injection of 70 per cent diodrast into arm vein. Left oblique view. A—arch of aorta. AL—left atrium. UAL—upper border of left atrium. X—approximate location of left recurrent laryngeal nerve.

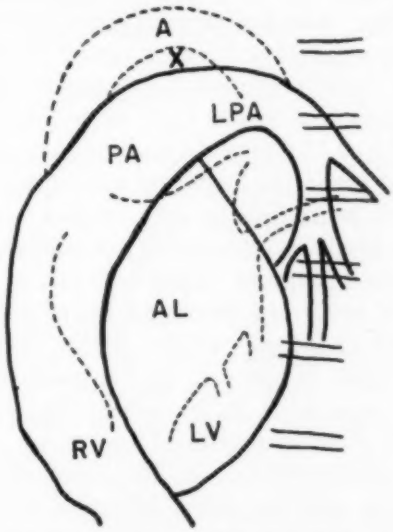

FIG. 9. *Case 2.* Diagram of superposition of angiocardiograms illustrated in figures 7 and 8. Labeling as in figures 7 and 8. Solid lines—diagram of angiocardiogram shown in figure 7. Dotted lines—diagram of angiocardiogram shown in figure 8.

findings were as follows: There was moderate left ventricular enlargement downward and to the left; an apical diastolic murmur was evident with an associated harsh mitral systolic murmur; the blood pressure was 90 systolic and 50 diastolic in each arm. The lung fields were clear. Laryngoscopic examination revealed flaccid paralysis of the left vocal cord. Roentgen-ray examination of the chest revealed the

cardiac silhouette to be of typical mitral configuration with enlargement in all diameters, particularly the longitudinal and oblique measurements. Esophageal compression was noted when barium swallow was given. The electrocardiogram revealed prolonged atrioventricular conduction (.23 sec.) as the only significant abnormality. Angiocardiograms (figures 7, 8 and 9) were done by Dr. George P. Robb, and his report is as follows: "The pulmonary valve and the main pulmonary artery are pushed cephalad toward the aortic arch by the elongated outflow tract of the right ventricle. The main stem of the pulmonary artery is enlarged throughout and measures 4.0 cm. in diameter (normal 3.0 cm.). At the bifurcation the diameter is still 4.0 cm. The left pulmonary artery as it passes beneath the aortic arch is also enlarged and measures 3.4 cm. in diameter. By superimposition of films the superior wall of the elevated and dilated left pulmonary artery seems to be in close contact with the overlying arch of aorta. The left atrium is enlarged in all diameters and extends to the right in the left anterior oblique view, displacing and compressing the superior vena cava and right auricular appendage. It is approximately 8.0 cm. in transverse and vertical diameters as compared to the normal values of 4.0 and 4.5 cm. Its concave upper border is far removed from the aortic arch by a distance of 3.5 cm. The thoracic aorta is poorly outlined because of two factors, the low concentration of diodrast in its lumen and the shadows of adjacent and overlying pulmonary veins. It is definitely small with a maximal transverse diameter of 2.5 cm. There is no evident displacement or distortion of the arch by the enlarged pulmonary artery or left branch."

Discussion

Left recurrent laryngeal nerve paralysis occurs very infrequently in heart disease. Fetterolf and Norris [2] who were particularly interested in this question encountered only one case among several hundred patients with cardiac disease. Reiche [3] noted only two cases among 300 patients with mitral stenosis. From a different point of view Scheifley and Smith [4] determined the incidence of mitral stenosis in a series of 223 cases of recurrent laryngeal nerve paralysis and found only 10 patients with mitral stenosis whereas New and Childrey [5] found only seven patients with mitral stenosis in a series of 322 cases of recurrent laryngeal nerve paralysis. Because of the infrequency with which heart disease is associated with recurrent laryngeal nerve paralysis it has been suggested that the association is purely coincidental.[6] This suggestion acquires some force from the fact that a large proportion of cases of recurrent laryngeal nerve paralysis is etiologically unexplained even after thorough study. Thus 33 per cent of the cases studied in one group [5] and 41 per cent of the cases studied in another [4] fell into this unexplained category. It is evident that if heart disease should occur by chance with these unexplained cases, an etiological relationship would be assumed. Nevertheless, the incidence of mitral stenosis is 10 times as great in patients with recurrent laryngeal nerve paralysis as in general hospital patients.[4] Furthermore, if the association were purely coincidental there should be no difference in the incidence of rheumatic heart disease among cases of left and right recurrent laryngeal nerve paralysis. Yet Scheifley and Smith [4] as well as New and Childrey [5] found all the cases of rheumatic heart disease associated with left recurrent laryngeal nerve paralysis and none associated with right recurrent laryngeal nerve paralysis.

This is what should be expected from an anatomical etiological association in view of the intimate anatomical relationship of the heart to the left recurrent laryngeal nerve, and its relative remoteness from the right recurrent laryngeal nerve. In the older literature there are some reports of right recurrent laryngeal nerve paralysis with rheumatic heart disease, but Fetterolf and Norris [2] found from a study of the literature that these were cases in which the left recurrent laryngeal nerve was also involved. Furthermore, they found no cases in which postmortem evidence was presented.

It may be accepted as established that the left recurrent laryngeal nerve is paralyzed in some way as a direct result of the heart disease. The explanations of the pathogenesis, however, have been varied. A common explanation of some of the older authors, and one which still is prevalent, was that the enlarged left atrium of mitral stenosis compressed the nerve. As long ago as 1911, however, Fetterolf and Norris [2] showed that it was next to impossible for the left atrium to impinge directly on the nerve. They pointed out that the nerve must be compressed between the aortic arch and the left pulmonary artery, and they believed that any condition which would dilate or force upward the left pulmonary artery, the left pulmonary vein or the left atrium would tend to produce nerve compression. These authors noted that some of the postmortem studies in the literature mentioned the obliterated ligamentum arteriosum, but they considered this of negligible importance. In those cases associated with a patent ductus arteriosus, the authors considered the important factor to be the resulting pulmonary artery dilatation. They believed that other explanations were either disproved by their anatomical studies or ill-founded. These other explanations included (1) traction on the ligamentum arteriosum and the nerve as a result of hypertrophy of the right ventricle and change in cardiac position, (2) compression of the nerve between a patent ductus arteriosus and the aortic arch, (3) compression of the nerve by peribronchial and peritracheal glands, enlarged as a result of congestive heart failure and (4) compression of the nerve between the left bronchus and the enlarged left atrium.

Notkin [7] reported a case with pulmonary artery dilatation in which he believed a lymph gland in the triangle formed by the aortic arch, the pulmonary artery and the ligamentum arteriosum contributed to compression of the nerve. He reviewed the literature up to 1924 and found only 17 cases with postmortem study. He concluded that the most important factor in the causation of the paralysis was either pulmonary artery dilation or pressure transmitted to the pulmonary artery by a dilated left atrium. He pointed out, however, that certain secondary factors might contribute to compression of the nerve such as thrombi in the left atrium, thrombosis of the pulmonary artery, arteriosclerosis of the pulmonary artery and aorta, and enlarged mediastinal glands. In a certain number of cases he believed that an initial neuritis occurred which was aggravated as the cardiac condition grew worse and which went on to degeneration as the nerve became compressed.

We are able to find only five case reports with postmortem study of rheumatic heart disease and left recurrent laryngeal nerve paralysis published since Notkin's [7] review. Klein [8] found mitral insufficiency rather than stenosis in his case with adhesive pericarditis at the base of the heart in the neighborhood of left atrium, aorta, and pulmonary artery. He believed that the pericarditis fixed the left atrium, preventing its usual posterior extension during enlargement and causing upward extension with pressure on the nerve through the displaced left bronchus. Reiche [8] found the pulmonary artery compressed and pushed aside by a greatly dilated left atrium which was filled with thrombi and which adhered to the aorta and the nerve. In Langeron's [9] case there was a Horner's syndrome as well as hoarseness. The left recurrent laryngeal nerve was embedded in dense scar tissue which also matted together all the other structures of the left side of the chest and was presumably due to healed mediastinitis. Alpert [10] found enormous dilatation of the pulmonary artery and its major branches and no enlargement of the left atrium. Eizaguirre [11] found a dilated left atrium filled with a large thrombus and a dilated pulmonary artery. He found the left recurrent laryngeal nerve compressed between the pulmonary artery and the aortic arch and believed that the large left atrium pushed the pulmonary artery against the aorta.

In 1934 King, Hitzig and Fishberg [12] reported three cases in which left recurrent laryngeal nerve paralysis was associated with congestive failure due to coronary arteriosclerotic heart disease. There was no rheumatic valvular disease in these cases. (Up to the time of this study almost all the reported cases had dealt with rheumatic heart disease and almost all of these with mitral stenosis.) In two of the cases postmortem studies were carried out. The authors attributed the nerve paralysis to compression by a dilated pulmonary artery, the latter being a consequence of the pulmonary hypertension resulting from left heart failure. They believed that the pulmonary artery dilatation was the important common factor in the cases of coronary arteriosclerotic heart disease with failure and rheumatic heart disease. They pointed out that the pulmonary artery dilatation might be dynamic rather than structural and that there might be little or no postmortem evidence.

Other forms of cardiac abnormality with pulmonary artery dilatation and left recurrent laryngeal nerve paralysis have been reported. These included interatrial septal defect [7, 13, 14, 15] and the Eisenmenger syndrome.[16, 17] The left atrium was not described in some of these reports, but where it was noted it was not enlarged, or enlarged only slightly.[13, 15]

In Case 1 of this report there was roentgenographic and postmortem evidence of pulmonary artery dilatation (figures 1 and 2) whereas in Case 2 the pulmonary artery dilatation was demonstrated by angiocardiograms (figures 7 and 9). The left atrial enlargement was slight in Case 1 and more pronounced in Case 2. The gross dissections in Case 1 showed that the portion of the nerve lying between the aortic arch and the pulmonary

artery was discolored reddish brown and flattened. The discoloration may be significant but flattening of the nerve has been observed in normal cases.[2] The dissection showed further that while the nerve could readily have been compressed between the left pulmonary artery and the arch of the aorta, it was quite remote from any contact with the left atrium (figures 2 and 3). None of the other possible causes of nerve compression mentioned in the literature and discussed above were present. The histologic studies of the nerve localized the site of compression quite clearly as being between the left pulmonary artery and the arch of the aorta. It is interesting to note that there was no significant stenosis of the mitral valve.

The preponderance of evidence seems to indicate that pulmonary artery dilatation is the primary cause of the left recurrent laryngeal nerve paralysis. While this was a common factor in most of the cases studied, including our own, other factors may or may not have been present. Whether or not left atrial enlargement plays a contributory rôle in some cases (by pushing the left pulmonary artery against the aorta), as some authors have suggested, is difficult to demonstrate. The fact that the paralysis has been observed in cases in which there was no significant left atrial enlargement would tend to minimize the importance of this factor. It cannot be denied that in certain cases other factors may be involved in addition to pulmonary artery dilatation; these have already been mentioned in the review of the literature.

It is a very puzzling fact that while pulmonary artery dilatation is common, associated left recurrent laryngeal nerve paralysis is rare. King, Hitzig and Fishberg [12] attempted to explain this discrepancy by the relation of the ligamentum arteriosum to the nerve. They believed that if the ligamentum is so situated as to fix the nerve, and keep it from slipping as the pulmonary artery dilates, it should favor compression of the nerve in the triangle formed by the arch of the aorta, the ligamentum arteriosum and the left pulmonary artery. These authors postulated that such an anatomical relationship is rare. Fetterolf and Norris,[2] on the contrary, indicated that such a relationship is usual. Their sections and dissections were carried out in cadavers pre-hardened by arterial injection of formalin thus preserving the original relations as well as possible. The essence of their description was as follows: The left recurrent laryngeal nerve hugs the aorta closely and passes under the arch either at the point at which the ligamentum arteriosum joins the latter or slightly anterior to this position. The ligamentum arteriosum is a fibrous cord, about 3 mm. thick and 2 cm. long, lies almost exactly in the anteroposterior plane of the body and ascends but slightly as it passes backward from the left pulmonary artery to the aorta. In or slightly anterior to the obtuse angle formed at its junction with the latter vessel lies the recurrent laryngeal nerve. The left branch of the pulmonary artery passes outward and markedly backward. Above and 4 mm. away from it is the beginning of the descending part of the aorta to which it is connected by the ligamentum arteriosum. The normal relations, then, seem

to provide quite well the conditions for compression of the nerve in the triangle formed by the aortic arch, the ligamentum arteriosum, and the left pulmonary artery. It would not seem to require much pulmonary artery dilatation to fix the nerve against the ligamentum arteriosum and permit compression between pulmonary artery and aorta. Why this does not occur more frequently cannot be explained at present. It is possible that there is individual variation in susceptibility of the nerve to pressure, and that in most instances the nerve withstands pressure from a dilated pulmonary artery without functional derangement.

Summary

Two cases of rheumatic heart disease associated with left recurrent laryngeal nerve paralysis are reported. Angiocardiographic studies were carried out in one case and postmortem studies in the other. The literature is briefly reviewed, and the cause of the paralysis is discussed. The primary factor is compression of the nerve by dilatation of the left pulmonary artery. In view of the relative frequency of pulmonary artery dilatation, however, the rarity of left recurrent laryngeal nerve paralysis remains unexplained.

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STUDIES ON VENOUS PRESSURE IN HEPATIC CIRRHOSIS *

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This work was undertaken to evaluate venous pressure measurements in diagnosis of cirrhosis of the liver. Only patients with classical clinical manifestations of cirrhosis were included in these studies. It is interesting that no study of pressure in the veins of the collateral circulation of the liver could be found in the medical literature.

Ten normal white subjects and 10 white subjects with cirrhosis, ranging in age from 23 to 81 years, were observed (tables 1 and 2). Measurements

Table I

Pressure within the Veins of the Antecubitus Region, Abdomen and Dorsum of the Feet of 10 Normal White Women Resting Supine

Subject No.	Age in Years	Vein				
		Antecubital	Abdominal		Pedal	
			Right	Left	Right	Left
1	67	95	105	110	120	125
2	25	125	160	135	100	110
3	27	100	100	115	105	100
4	40	65	100	115	85	90
5	31	105	110	100	125	130
6	40	115	135	120	125	120
7	30	95	140	135	100	115
8	24	120	130	110	110	100
9	26	110	120	110	130	120
10	23	100	85	70	120	130
Max.		125	160	135	130	130
Min.		65	85	70	85	90
Mean		103	119	112	112	114

were obtained with the subjects in the supine position and with the use of apparatus described in earlier publications.[1, 2] The antecubital veins, the superficial abdominal (thoracoepigastric, superficial epigastric and superficial circumflex iliac) group of veins and the veins of the dorsal venous rete of the feet were the sites of study. Determinations were obtained just prior to and immediately following paracentesis. At all times measurements were

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TABLE II

Pressure within the Veins of the Antecubitus, Abdomen and Dorsum of the Feet of 10 Patients with Classical Hepatic Cirrhosis

(a) Before Paracentesis

Subject No.	Sex	Age in Years	Vein				
			Antecubital	Abdominal		Pedal	
				Right	Left	Right	Left
11	F	81	120	240	225	195	190
12	M	58	140	210	205	160	170
13	M	62	65	110	100	100	110
14	M	52	80	65	90	180	170
15	M	47	85	75	80	60	75
16	M	55	95	220	180	130	125
17	M	46	110	130	140	120	130
18	M	54	105	110	100	115	130
19	F	40	40	130	130	115	100
20	M	48	85	115	125	115	100
Max.			140	240	225	195	190
Min.			40	65	80	60	75
Mean			93	141	138	129	130

(b) After Paracentesis

Subject No.	Vein					Quantity, Liters
	Antecubital	Abdominal		Pedal		
		Right	Left	Right	Left	
11	110	165	155	125	130	8.8
12	120	160	160	125	135	3.2
13	65	100	85	95	90	3.6
14	80	25	40	60	50	14.3
15	85	85	90	115	110	3.0
16	90	200	170	110	120	2.8
17	100	90	100	110	120	9.0
18	110	95	90	115	120	1.5
19	45	90	95	110	105	1.0
20	90	100	110	110	105	5.4
Max.	120	165	170	125	135	
Min.	45	25	40	60	50	
Mean	90	111	110	108	109	

made at the phlebostatic axis and level. The quantity of ascitic fluid removed varied considerably, the minimum being one liter and the maximum 14.3 liters (figure 1).

Analysis of results showed a wide range of variations in the values for venous pressure, with overlapping of the values for normal and abnormal subjects. The average pressure in the abdominal and pedal veins of the cirrhotic group tended to be greater before paracentesis than in the normal subjects (table 2 and figure 1). There was a consistent, though slight,

decrease in the pressure in the abdominal veins after paracentesis. There were no uniform changes in the pressure in the antecubital and pedal veins following removal of ascitic fluid, although the pressure within the veins of the foot usually decreased (table 2 and figure 1). Individual variations for the normal subjects are shown in table 1. These are in agreement with values previously reported.[3]

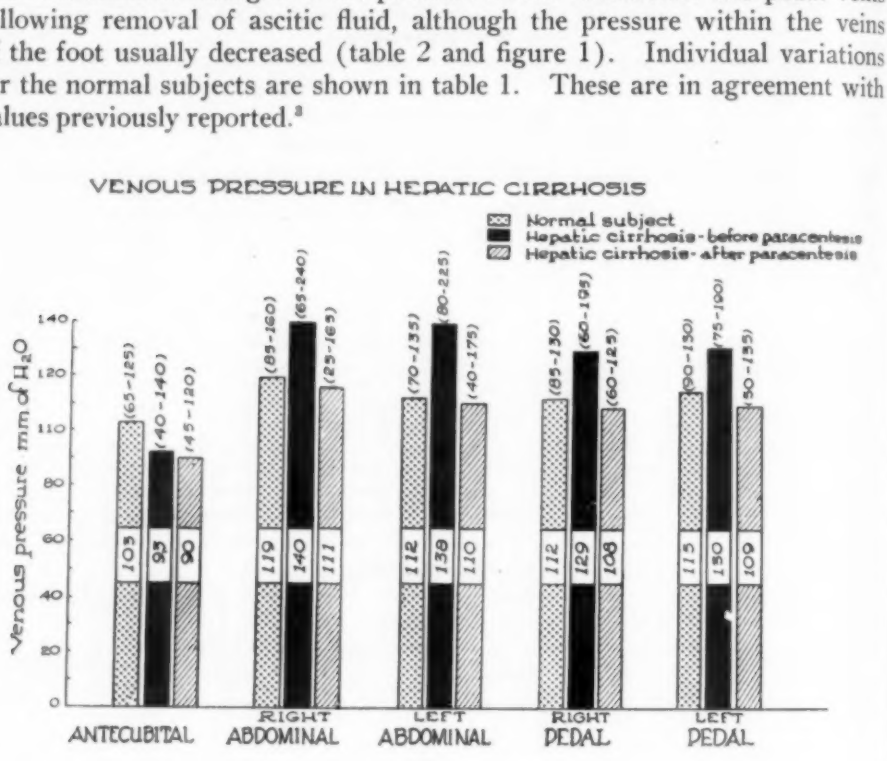

FIG. 1.

Patient numbers 11, 12, 17 and 19 experienced a decided drop in venous pressure, especially in the abdominal and pedal veins, following removal of 8.8, 3.2 and 1 liters of ascitic fluid respectively. However, in patient numbers 17 and 19 the pressure in the veins of the abdomen and feet was reduced to within normal range following paracentesis. Patient number 13, who had approximately the same amount of fluid removed as patient number 12, presented no initial elevation of venous pressure and no change following paracentesis. Patient number 14 exhibited a considerable fall in venous pressure in the veins of the abdomen and feet following paracentesis, even though initial pressures in the abdominal veins did not exceed the normal range. Patient numbers 16, 18, and 20 showed no appreciable change in venous pressure following removal of ascitic fluid.

Some of the subjects revealed a decrease in pressure in the veins of the abdomen and feet following paracentesis, the final pressures remaining elevated, as might be anticipated, since there is obstruction to flow in the portal vein in hepatic cirrhosis. However, results were too inconsistent to permit the use of venous pressure determinations as reliable diagnostic evidence in

suspected cases of hepatic cirrhosis. The changes in pressure following paracentesis were sufficient to demonstrate the value of this procedure in improving the hemodynamics of the venous circulation below the level of the diaphragm. Failure of the pressure to rise in the abdominal veins in some of the patients with hepatic cirrhosis indicates lack of overloading and adequacy of the parahepatic collateral circulation. It is possible that the entrance of the portal venous blood to the collateral vessels may be incomplete, even though these vessels can drain the blood adequately. The ascites in these patients is most probably related to factors other than venous hypertension of the portal system.

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ACUTE MERCURY POISONING: TREATMENT WITH BAL AND IN ANURIC STATES WITH CONTINUOUS PERITONEAL LAVAGE *

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The past 30 years have seen the introduction of a number of schemes for the treatment of acute bichloride of mercury poisoning. Until recently, none of them has proved to be generally effective in preventing death in severe cases.

BAL (2, 3-dimercaptopropanol) has been found to be an effective antidote for mercury poisoning. Peritoneal lavage as recently improved is a satisfactory procedure for the treatment of temporary anuric states. These advances make possible the formulation of a therapeutic regime which should enable us to save most of the patients who ingest and retain fatal doses of mercuric salts—even those seen too late for proper antidotal treatment.

We have recently had an opportunity to observe modern therapy in such a patient and believe that the experience will serve as the basis for formulating a general therapeutic plan.

General Considerations

A number of factors are of significance in the consideration of cases of mercury poisoning. The foremost of these is the dose of the salt ingested and retained. Experimental animals do not survive when 4 mg. per kilogram is given intravenously or when, with the prevention of vomiting, 30 mg. per kilogram is given orally. In man, vomiting follows the ingestion of mercury bichloride with such regularity that it has served to separate real from spurious cases. The effect of the salt is to a large extent modified by the early onset of emesis; however, it is generally believed that the ingestion of 1 gram regularly results in serious poisoning [1, 2, 3, 4, 5] and that 1.5 grams will commonly lead to a fatal termination.[6]

For various reasons only about half of the patients who appear at a hospital with a history of bichloride of mercury ingestion develop significant symptoms of poisoning and of the half who develop symptoms half, or 25 per cent of the whole group, fail to survive.[5] This makes it very difficult to interpret the results in small series of cases.

Bichloride of mercury is a simple protoplasmic poison which produces tissue necrosis whenever and wherever critical concentrations of the drug obtain. The principal pathological lesions are related to the sites by contact during absorption or by concentration in the excretory processes. The

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earliest lesions are the direct result of the contact of the salt with the mucous membranes of the mouth, stomach and upper small intestine, or occasionally the vaginal mucous membranes. Absorption is rapid and in a very short time injurious concentrations occur in the renal tubules and in the colon where the drug is concentrated by excretion. Very large doses of the drug lead to death in a period of one to two days, primarily as a result of shock-like states. Of those who do not initially show this reaction there is a group of mild cases who may show little or no evidence of poisoning. Still another group, who usually have vomiting and diarrhea as early predominant symptoms, develop signs of renal damage, often in the form of anuria which may occur either early or late in the course of their illness.

Hull and Monte [5] have found that the prognosis is extremely grave when patients have a period of anuria lasting 24 hours or more or when they develop a blood nonprotein nitrogen level above 125 mg. per cent. Peters, Eisenman and Kydd [4] reported a mortality rate of 25 per cent in a series of cases in which all fatalities experienced a period of anuria and all survivors escaped even transitory anuria. Rosenbloom [7] in 1915 demonstrated that while mercury could be found in practically every tissue of the body in fatal cases, the most important lesion in serious cases surviving the immediate shock stage is the necrosis of the epithelium in the convoluted tubules of the kidney. Fortunately, the tubular epithelium of the kidney has remarkable powers of regeneration,[4] and healing may occur without residual impairment of renal function. For this reason, the treatment of patients with anuria should be directed toward the prevention of death due to retention of waste products until the tubular epithelium regenerates and renal function returns. This generality was well expressed and emphasized by Hayman and Priestley.[8]

Past Treatment Regimes

Lambert and Patterson [9] in 1915 presented a regime for the treatment of acute mercury poisoning which aimed at the prevention of the reabsorption of the excreted mercury. This plan involves gastric lavage, colonic irrigations, and the administration of large amounts of alkaline solutions and milk by mouth. Only two of their 16 cases so treated died. Weiss [10] in 1917 reported 25 cases which were apparently mild but were successfully treated by a modification of the above plan. Others have been unable to achieve equivalent results. Peters, Eisenman, and Kydd [4] strongly advocated measures aimed at the prevention of shock, dehydration and salt depletion. Although the mortality rate has not been greatly reduced by such measures, it is now generally accepted [2, 3, 4, 8, 9, 11, 12, 5] that every effort should be made to keep these patients, as near as possible, in a normal state of fluid and electrolytic balance.

Various drugs have been used to combat the poisoning from bichloride of mercury. These were usually employed on the principle of the therapeutic

agent combining with mercury to produce an excretable nontoxic substance. These were usually sulfur containing drugs, among which were calcium sulfide, hydrogen sulfide, sodium thiosulfate, and sodium formaldehyde sulfoxylate. The latter drug, which was introduced by Rosenthal,[13] is still being used rather widely with variable results. Hull and Monte,[14] who treated 40 patients with this drug, found the results no better than those obtained by other therapeutic measures. Muir, Stenhouse and Becker [15] could not protect rabbits from mercury poisoning by giving sulfur containing compounds after mercury poisoning. They did, however, demonstrate that some protection could be obtained when the therapeutic agents were given before the poisoning was produced. Mintz [16] in 1933 reviewed the literature on the treatment of acute mercury poisoning and stated, "in the interval before the local physician has arrived, which I feel is more than 13 minutes, the patient has either saved himself by early vomiting or else has absorbed the lethal dose, provided, of course, that a sufficient quantity has been taken."

Although a number of surgical procedures have been advanced for the treatment of the various lesions, none of them has been significantly effective. Anderson [17] and Berger, Applebaum and Young [1] tried colostomy with colonic irrigation. Mintz [16] expressed the opinion that their statistics were far from convincing and very aptly asked if high colonic irrigations could not accomplish the same purpose.

Renal decapsulation has been used for many years in the treatment of anuria, usually on the basis of relieving the pressure on the renal tubules. It is true that there are isolated reports of anuric patients who coincidentally or otherwise improved following this procedure. However, the unsuccessfully treated cases by far outnumbered the successes and it would seem, in general, the results do not justify renal decapsulation, especially in view of the trauma and shock associated with the procedure.

Johnstone [18] in 1931 successfully treated two patients with anuria secondary to mercury poisoning by venesection and multiple transfusions. Hashinger and Simon [19] in 1935 used "exsanguination" and multiple transfusions successfully in the treatment of a patient with a severe intoxication and uremia. This procedure may have been of considerable value prior to the use of BAL and peritoneal lavage.

Recent Advances in Therapy

BAL (2, 3-dimercaptopropanol) is a product of British war research; developed principally by Peters, Stocken and Thompson [20] to combat the toxic effects of arsenic. They believe that the arsenic in combining with a tissue –SH group inactivates an enzyme system vital to cellular metabolism. BAL combines with the arsenical and effectively prevents this cellular damage. These studies led to investigations of the effects of this drug on poisoning by other heavy metals.[20, 21, 22, 23] As a result of these studies proof now

exists that mercury also inactivates a cellular enzyme system and that these effects may be prevented by the administration of BAL. It seems probable from the above studies that while BAL is most effective when given early it may be of value even late in mercury poisoning. This has been borne out experimentally [22, 23] as well as clinically [6] and it seems very likely that BAL can reactivate enzyme systems already poisoned by mercury.[23]

Longcope and Luetscher [6] recently reported very dramatic results in BAL treatment of 42 patients who had ingested from .5 to 20 grams of bichloride of mercury. All but two of these patients survived. One exception, a patient who did not receive BAL until 13 hours had elapsed, died on the ninth day after poisoning. The other exception was a woman who had taken 2 grams of bichloride of mercury six hours before admission. These workers emphasized the great importance of therapy within the first few hours after the ingestion of mercury and the continuance of such therapy for several days thereafter. For a comparison they pointed out that before the use of BAL they had treated 86 patients by former methods within four hours of poisoning and that, of these, 27 had died. Of the 24 patients in the BAL treated series, who received therapy within 4 hours, there were no deaths. These authors employed an initial intramuscular injection of 300 mg. of BAL followed within the first 12 hours by two or three additional injections of 150 mg. each. During the second 12-hour period their patients usually received one and often two 150 mg. injections after which time they were usually given two injections of 150 mg. each day for one to two days, depending on the condition and response of the patient. Their patients received a total of between 1200 and 2870 mg.

As a result of the above experimental and clinical studies, it seems highly probable that a really effective antidote for acute mercury poisoning has been found. The prognosis is apparently good provided the patient is treated within the first four hours, even following the ingestion of relatively large amounts of bichloride.

There still remains a group of these patients who, not having received BAL therapy within the first few hours, will develop anuria secondary to tubular injury. These patients will ultimately die unless something can be done to provide a temporary means of controlling their uremia until renal function returns.

For many years it has been known that the organic solutes and electrolytes in plasma would dialyze across the peritoneal membrane.[24] Bliss showed that the lives of rabbits, made anuric with bichloride of mercury poisoning, could be prolonged and the mortality could be reduced by peritoneal irrigations. Prior to 1940, attempts to treat humans by peritoneal irrigations were unsatisfactory [27, 28, 29] because of inadequate control of electrolyte balance and inability to effectively treat the peritonitis that is so apt to develop.

In 1934, Balazs and Rosenak [29] attempted peritoneal irrigation in two patients with anuria secondary to mercury poisoning. Though their patients died, they temporarily prevented the development of azotemia. Their failure was probably due to the fact that a simple glucose solution was used for the irrigations and the periods were far too brief.

Recently two separate groups of workers have revived interest in this procedure and have done much to eliminate many of the hazards of peritoneal irrigations.

Abbott and Shea,[30] after animal experimentation, postulated that this procedure could be effectively employed in patients with anuria following bichloride of mercury poisoning, hemolytic transfusion reactions, toxic nephrosis due to sulfonamides, or developing as a part of the "crush syndrome." They studied solutions of varying composition for peritoneal lavage and came to the conclusion that a solution with a balanced salt mixture made slightly hypertonic with glucose was most effective. They found that waste products and "presumably other toxic elements," could be removed from the blood stream by intermittent peritoneal lavage and that their nephrectomized animals could be kept in a relatively normal state of fluid and electrolyte balance for a week or more.

Independently, Seligman, Frank and Fine [31] found that peritoneal lavage was 40 to 70 per cent as effective as normal kidney function and that nephrectomized dogs with uremia could be improved and could be kept alive 3 to 10 days. Their animals died of peritonitis but did not redevelop uremia while under treatment. They used a modified Tyrode's solution with heparin to prevent intraperitoneal fibrin deposition and penicillin and sulfadiazine as a prophylaxis against infection. They recommended 20 to 50 ml. per minute as the optimal rate of flow for maximum urea clearance. After the azotemia, which developed in pre-lavage period, was corrected, peritoneal irrigations for 8 to 10 hours each day prevented the reaccumulation of waste products.

Recently this group reported [32] the results of peritoneal irrigation in four patients. The first of these had azotemia secondary to an inoperable uterine carcinoma but was temporarily improved by the lavage. Attempts to control the uremia by other forms of dialysis had been ineffectual. The second, a 14 year old girl with anuria due to a hemolytic transfusion reaction, was successfully treated for the azotemia but subsequently died from pulmonary embolism. The third, a 51 year old man with anuria secondary to sulfonamide poisoning, was controlled by peritoneal lavage until the fourteenth day of anuria when his urinary function returned. The last, a 19 year old girl with anuria from a hemolytic transfusion reaction, died after her course was complicated by the development of shock and pulmonary edema.

They concluded from these experiences that it would be desirable to make the irrigating fluid hypertonic with 2 per cent dextrose to prevent the tendency to develop pulmonary edema, a complication encountered in three of the four cases.

Case Report

A 17 year old white female was admitted to the Pediatric Service of Vanderbilt Hospital * on August 1, 1946, with anuria of five days' duration.

Five days prior to admission she took two .5 gram tablets of bichloride of mercury. Ten minutes later she developed severe nausea and vomiting and her mouth and throat became sore. She stated that she had vomited every time she took fluids or ate during these five days. She did not void after the ingestion of the mercuric salt.

Two days after the onset of anuria a physician was called to treat her sore throat. A diagnosis of diphtheria was made, confirmed by smear and culture, so she was given 40,000 units of diphtheria antitoxin intramuscularly. It was only after this lapse of time, four days, that she admitted taking the bichloride of mercury. Her physician recommended hospitalization when the anuria persisted another day.

Physical Examination: Temperature 99°, pulse 96, respirations 22, blood pressure 132/90. The patient was a tall, slender girl who lay quietly in bed, complaining occasionally of pain in her throat and abdomen. She was slightly but definitely lethargic. She was coöperative except during her bouts of vomiting when she screamed out with pain. She was moderately dehydrated rather than edematous and there was evidence of recent weight loss. Her buccal mucosa showed several 1 by 1 cm. ulcerated areas covered by a soft gray membrane and surrounded by an area of redness approximately 1 cm. in width. The tonsils were enlarged and covered by a similar membrane and the posterior pharynx showed extreme redness with several large ulcerated areas. The cervical lymph nodes were moderately enlarged and tender. The heart was normal in size and sounds with a rate of 80 to 100 beats per minute and the electrocardiograms showed no abnormalities. The lungs were clear. There was generalized abdominal tenderness.

Admission laboratory studies showed: red blood cells 2.89 million, hemoglobin 10.5 gm., and white blood cells 27,700; bleeding time, coagulation time and clot retraction time were within normal limits. The blood non-protein nitrogen was 203 mg. per cent, plasma CO_2 combining power 32.4 volumes per cent, plasma chloride 72.9 milliequivalents per liter and plasma phosphorus 14.8 mg. per cent. Catheterization yielded approximately 30 c.c. of very thick, cloudy, mucoid material having no resemblance to urine.

The patient was immediately (on the fifth day) started on BAL therapy, receiving 225 mg. every four hours for 14 doses, 3.15 grams in 56 hours. The dosage was then reduced to 225 mg. twice daily and was continued until the end of the seventeenth day to a total of 7 grams.

Because of secondary infection of her pharyngeal lesions, she was given 15,000 units of penicillin every four hours and, in varying dosage, this antibiotic was continued for 35 days.

For the prevention of excessive edema parenteral fluids were limited. Attempts to administer fluids by mouth were unsuccessful because of continued nausea and vomiting. She was given 50 per cent dextrose intravenously on several occasions in a futile attempt to establish diuresis.

After the sixth and seventh days it was apparent that the patient was getting much worse. Complete anuria continued while lethargy became more marked. Her plasma chloride level and CO_2 combining power remained essentially unchanged, but her blood nonprotein nitrogen level had risen to 240 mg. per cent. It was felt that she could not possibly survive unless her uremia could be temporarily controlled and, with this in mind, continuous peritoneal lavage was initiated.

Under local anesthesia and with the patient in bed, an incision was made below and parallel to the right costal margin and a No. 24 mushroom catheter was inserted.

* Admission to the Pediatric Service was due to the misrepresentation of her age.

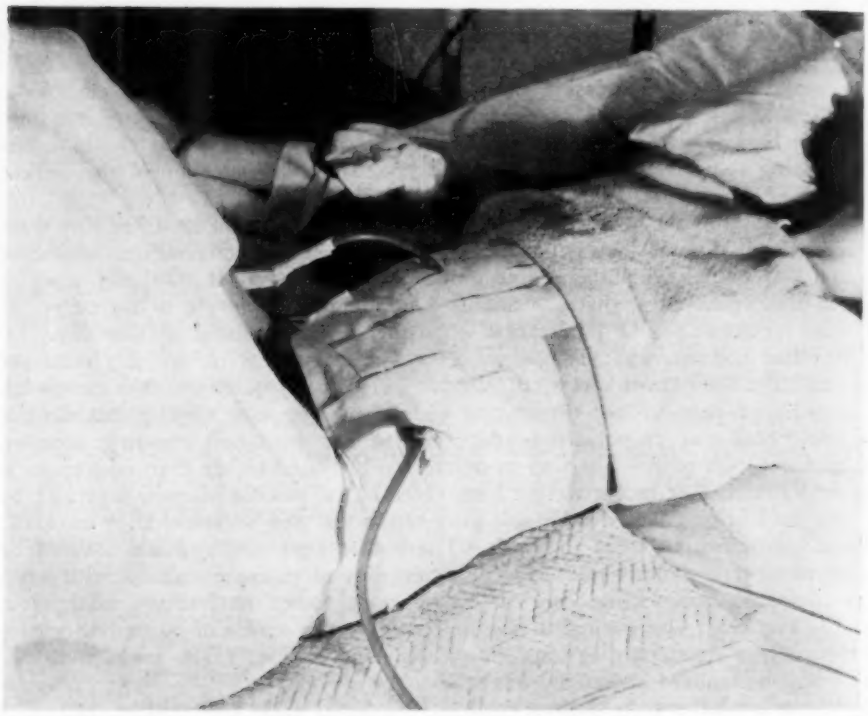

FIG. 1. Photograph of peritoneal inflow and outflow tubes in place.

The tissues were closed snugly about the catheter with fine interrupted silk sutures. Another incision approximately ½ inch in length was made just medial to the left anteriosuperior crest of the ilium and a rather large paracentesis trocar was pushed through the peritoneum. The trocar was withdrawn from its casing and replaced by a closely fitting suction tip. A similar closure was made here. Peritoneal irrigation was initiated with 1 liter of solution per hour being allowed to flow by gravity through the mushroom catheter, over the peritoneal surfaces, and out of the outlet tube in the left lower quadrant (figures 1 and 2).

TABLE I

Peritoneal Irrigation Fluid*
(Solutes in gm. per liter water)

Sodium chloride	6.10
Calcium chloride	0.23
Potassium chloride	0.35
Sodium phosphate (monobasic)	0.07
Magnesium chloride	0.05
Sodium bicarbonate	2.20
Dextrose†	30–50
Penicillin (units)	2000–10,000
Sodium heparin	0.002

* This solution is a slight modification of "A" solution that was used experimentally and ecommended by Abbott and Shea.[20]

† 50 to 100 gm. of dextrose per liter of solution was used in our case; however, 100 gm. per liter produced excessive dehydration and shock. By using 50 gm. per liter, a very good balance between peritoneal intake and output was obtained.

The solution employed was modified from "Solution A" of Abbott and Shea.[30] Their solution was made hypertonic by the addition of 10 to 20 grams of dextrose per liter. Through error we employed 10 per cent dextrose, or 100 grams per liter, in the initial stage of irrigation. Table 1 shows the composition of our solution after correcting this error.

FIG. 2. Photograph of patient during peritoneal irrigation.

During the first 36 hours of this period the patient received intraperitoneally 20,000 c.c. of solution, while the return from the peritoneal cavity was 25,330 c.c. At this time she developed shock as represented by a precipitous fall in blood pressure,

rapid pulse rate, disorientation, increase in total serum protein, and a rise in the hemoglobin to 15 gm. This complication was overcome by the administration of large amounts of parenteral fluids including whole blood and plasma and by reducing the dextrose content of the peritoneal irrigation solution to 50 gm. dextrose per liter. After this step was taken no further difficulty was encountered which could be attributed to hypertonicity of the irrigation solution.

A very good balance between peritoneal inflow and outflow was obtained and during the six-day period of peritoneal irrigation the total peritoneal inflow was 69,000 c.c. with 72,800 c.c. outflow. 14,640 c.c. of plasma, whole blood, and crystalloid solutions were administered parenterally during that time and 3000 c.c. of fluids were retained by mouth.

Thirty-six hours after the institution of peritoneal lavage the blood nonprotein nitrogen had fallen to 144 mg. per cent and she began retaining fluids by mouth.

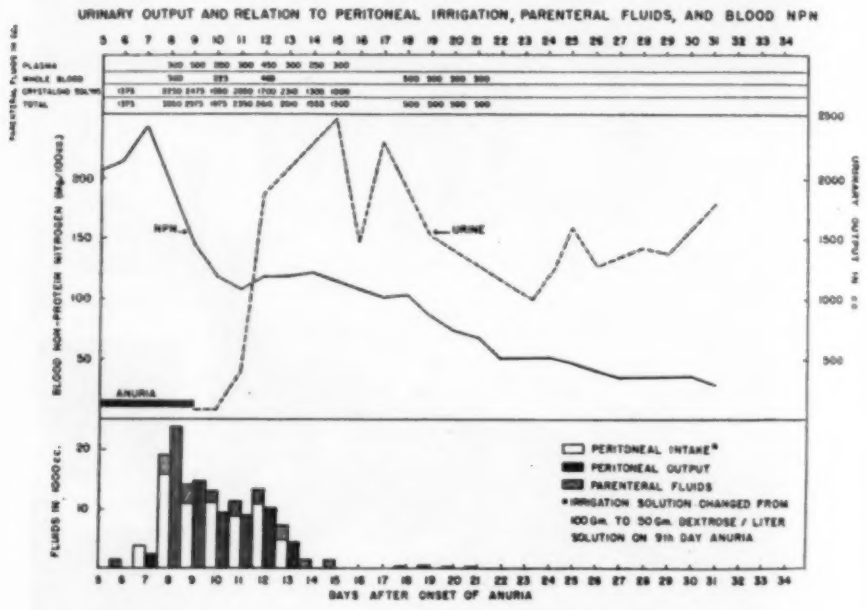

CHART 1.

On the ninth day, three days after the irrigation was started, she voided 90 c.c. of cloudy urine. Her subsequent urinary output was 90 c.c. on the tenth day, 500 c.c. on the eleventh day, and 1850 c.c. on the twelfth day. Thereafter output increased daily as did her fluid intake by mouth. The blood nonprotein nitrogen rapidly decreased as can be seen in chart 1.

On the eleventh day the patient developed a temperature elevation to 101.2° and the following day to 101.4°. She vomited on several occasions and complained of generalized abdominal pain. No peristalsis could be heard on examination of the abdomen, and it seemed apparent that she had peritonitis and paralytic ileus. Wangensteen's suction was started and she was given intramuscular streptomycin, 4 gm. daily in divided doses.

She had been on penicillin intramuscularly and peritoneally throughout the procedure with a blood level, before the development of peritonitis, of .435 unit per c.c.

Prior daily cultures of the peritoneal fluid had revealed no organisms but the culture taken just before the administration of streptomycin showed a strain of *B. pyocyaneus* which was subsequently found to be sensitive to 8 units of streptomycin per c.c. On the above dosage the blood streptomycin level reached 32 units per c.c. In spite of general improvement, the odor of pyocyaneus could be detected throughout the patient's room on the second day of peritonitis and her abdominal dressings were stained with a foul smelling greenish material. She improved rapidly on streptomycin therapy and by the third day all signs of peritonitis had disappeared.

By the thirteenth day she was voiding approximately 1500 c.c. every 24 hours, blood non-protein nitrogen was 118 mg. per cent and other blood chemistry values were approaching normal limits. It was decided that the patient's renal function was sufficient to maintain life and would probably continue to improve so peritoneal irrigation was discontinued.

As the patient recovered from paralytic ileus, she began having frequent loose, foul smelling, bloody stools. This continued from the sixteenth to the twenty-second

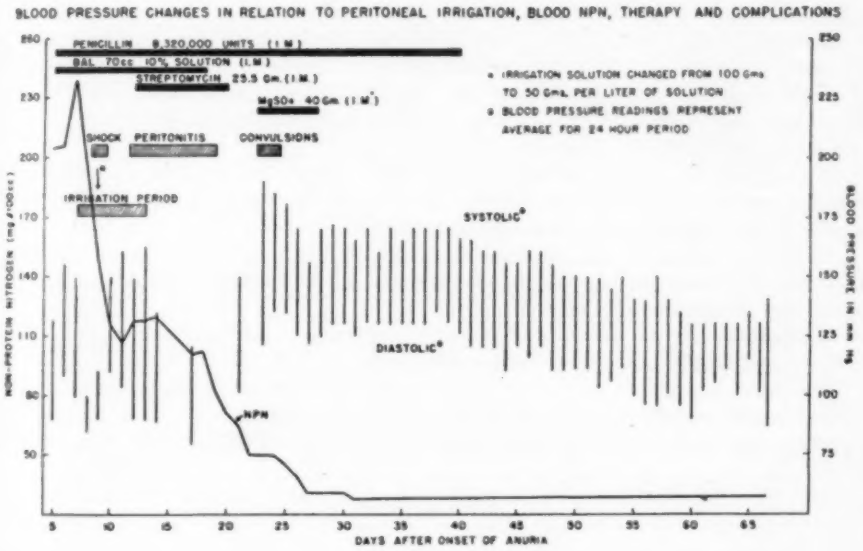
BLOOD PRESSURE CHANGES IN RELATION TO PERITONEAL IRRIGATION, BLOOD NPN, THERAPY AND COMPLICATIONS
PENICILLIN 8,320,000 UNITS (I.M.)
BAL 70cc 10% SOLUTION (I.M.)
STREPTOMYCIN 25.5 Gm. (I.M.)
MgSO4 40 Gm. (I.M.)
SHOCK
PERITONITIS
CONVULSIONS
IRRIGATION PERIOD
a IRRIGATION SOLUTION CHANGED FROM 100 Gms TO 50 Gms. PER LITER OF SOLUTION
b BLOOD PRESSURE READINGS REPRESENT AVERAGE FOR 24 HOUR PERIOD
SYSTOLIC
DIASTOLIC
NPN
NON-PROTEIN NITROGEN (mg. %)
BLOOD PRESSURE IN mm. Hg
DAYS AFTER ONSET OF ANURIA

CHART 2.

day and then ceased rather abruptly. Sigmoidoscopy was performed on the twenty-second day but no areas of ulceration or bleeding could be visualized.

Stool specimens collected from the eleventh through the seventeenth day (almost entirely from the sixteenth and seventeenth days of her illness) contained 20 to 25 mg. of metallic mercury.

In general she improved until the twenty-third day when she complained of inability to see and within 10 minutes began to have an extremely severe generalized convulsion. At this time her blood pressure, which previously ranged from 105/60 to 155/40, was found to be 194/120. She was started on treatment with intramuscular magnesium sulfate which temporarily relieved the arterial spasm and produced a definite decrease in her blood pressure. On the following day she was again rational but complained intermittently of inability to see. She continued to receive magnesium sulfate and, over a period of five days, received a total of 40 gm. At this time her blood pressure was still approximately 170/125. A cold pressor test and deep sedation

with intravenous sodium amytal produced no appreciable fluctuation of blood pressure. Her blood pressure did, however, fall slowly and progressively throughout the remainder of her hospitalization and was 130 mm. Hg systolic and 100 mm. diastolic when she was discharged on the sixty-fifth day. One month after discharge from the hospital the blood pressure was 117/72. The blood pressure changes during hospitalization may be seen in chart 2.

In the period of convalescence she developed a mild hypochromic anemia which responded well to iron therapy.

On the thirty-first day her blood nonprotein nitrogen was 28 mg. per cent and all other plasma chemistry values were within normal limits. Her urine was clear and straw-colored with a pH of 6.0, albumin negative, and sugar negative. Microscopic examination of an uncentrifuged specimen revealed 1 white blood cell per high power field and no other cells, casts, or crystals were noted. Specific gravity of urine fluctuated between 1.010 and 1.022. Intravenous phenolsulfonphthalein test showed 5 per cent dye recovered in 15 minutes, 20 per cent in the 30 minute specimen, 20 per cent in the one hour specimen and 15 per cent in the two hour specimen, or a total of 60 per cent in two hours. Intravenous pyelography showed the kidneys to be of average size, shape and position with good concentration of the dye bilaterally and with fairly complete filling of the calyces, pelves and upper ureters bilaterally. There was some blunting and dilatation of the calyces and on the upright film there was delayed drainage bilaterally. Repeated urine cultures yielded no growth.

Electrocardiography showed no abnormality.

During her illness the patient did not have one of her regular menses and developed a rather heavy growth of hair over her entire body. Later her menses recurred and the hirsutism decreased progressively.

At the time of discharge on the sixty-fifth day her appetite was good, she had no complaints, and was gaining weight consistently. The hospital course, complications, and therapy are shown in charts 1 and 2.

A tabulation of the changes in plasma constituents and fluid exchange occurring during hospitalization is shown in appendix table 1.

The patient returned to the outpatient clinic 30 days after discharge in apparent excellent health and having gained 20 lbs. in weight. The blood non-protein nitrogen was 28 mg. per cent, a random urine specific gravity was 1.022 and her blood pressure was 117/72.

Discussion

A number of errors were made during this experience with peritoneal irrigation, and we believe that many improvements in the technic can be outlined.

An abundance of trained personnel is necessary in order to manage this procedure properly. Our patient required the constant attendance of at least one nurse and an immediately available physician. On many occasions several members of both the house staff and nursing staff were occupied with this one patient.

Extreme care should be taken in the preparation of the patient and the selection of the equipment prior to the institution of peritoneal lavage. A completely aseptic technic should be observed at all times in manipulation of the tubing, bandages, changing of the reservoir, etc. Large reservoirs such as 15 liter flasks would lessen dangers of contamination by reducing the number of changes involved. As suggested by Fine and his group [32] a sump

Table II

Changes in Plasma Constituents and Fluid Balance

TABLE II

Changes in Plasma Constituents and Fluid Balance

Days after Onset of Anuria	Blood N.P.N. mg./100 c.c.	Plasma CO_2 Vol. %	Plasma Protein gm./100 c.c.	Plasma Chlorides m.eq./liter	Plasma Phosphorus mg./100 c.c.	Blood Sugar mg./100 c.c.	Hgb. gm.	$NaHCO_3$ I.V. in gm.	Fluid Intake P.O. in c.c.‡	Urine Output in c.c.	Irrigation Fluid		Parenteral Fluids in c.c.			Total
											Intake in c.c.	Output in c.c.	Plasma	Whole Blood	Crystal-loid Solutions	
5	203	32.4		72.9	14.8		10.5		−340	0						
6	212			69.9	11				−580	0					1375	1375
7	240	34.4	5.43	71.7	10.7	1180	12		460	0	4000[1]	2235				
8			6.97				14.5		1040	0	16000[1]	23095	300	500	2250	3050
9	144	31.2	6.02	80.4			15	12.5	963	90	11000†	14200	500		2475	2975
10	116	36.2	5.30	82.5	4.7	395	14		−350	75	11000	9485	200	225	1550	1975
11	106	33.4	4.97	87.6	5.6	139	11	20.0	75	380	9000	9250	300		2050	2350
12	118	53.2	4.5	86.4	7.0	118	11	14	−175	1841	11000	10120	450	465	1700	2615
13	118	89.9	4.98	87.3	7.4	166	11	4	425	595*	5000	4420	300		2310	2610
14	120	77.7	4.93	95.1	7.4	110			1600	435*			250		1305	1555
15									2325	2470			300		1000	1300
16	106	60.6	5.36	107.7	5.6	110			2350	1450						
17	100	49.4	4.76	110.7	4	102	8		3825	2265						
18	102	52.2	4.82	102.4	3.5	98			2350	1910				500		500
19	84	49.5	5.24	112.5			6		1160	1560				500		500
20	72	50.4	5.27	111.3	2.6	90	8		1170	760*				500		500
21	67	52.2	5.96	111.3	3.6	93	10.5		1950	700*				500		500
22	49	50.4	5.68	108.3	3.3	84	12		1130	380*						
23							12		700	955						
24	50	50.4	6.37	109.3	3.3	84			1600	1225						
25	45								1550	1570						
26	39								1830	1240						
27	31						11.5		1750	850*						
28									2000	1400						
29									1150	1350						
30	33								2225	2225						
31	28		5.52						1510	1510						
Total											68000	72805	2600	2190	14640	20430

[1] Irrigation fluid contained 100 gm. dextrose per liter solution.
† Irrigation fluid through remainder of irrigation period contained 50 gm. dextrose per liter solution.
* Incontinent or urine mixed with water stools.
‡ A deficit of fluids in this column represents excessive emesis.

drain * should be used as an outflow tube. They used an elaborate set-up for keeping the irrigation solution warmed to a temperature of 40 to 45° C. During the greater part of the irrigation period, we allowed the fluid to flow into the peritoneal cavity at room temperature and the patient experienced no discomfort. We are of the opinion that warming the solution is not necessary.

We believe that the irrigation solution should be made hypertonic by the addition of 30 to 50 mg. dextrose per liter in order to facilitate the abstraction of the excess interstitial fluid and solutes, and to reduce the risk of developing pulmonary edema. This increased glucose will also contribute to the satisfaction of the caloric requirements of these patients (several hundred calories from the glucose can be furnished the patient each day). This, of course, should be subject to individual variations and the dextrose content of the irrigating solution should be adjustable. The aim should be toward a balance between the peritoneal inflow and outflow and this is, of course, dependent on the tonicity of the irrigating solution. A step in the direction we have indicated was made by Fine and his group [32] suggesting an increase from 0.15 per cent glucose to 2 per cent.

Facilities should be available for frequent determinations of blood nonprotein nitrogen, plasma CO_2, plasma protein, plasma chloride, hemoglobin values, and at times other special determinations. We found that, in the process of peritoneal irrigation, fluid and electrolyte shifts occurred so suddenly that physical examination alone was apt to be misleading.

Sodium sulfadiazine probably should be added to the irrigation solution, except where the treatment is used for anuria due to sulfonamide intoxication. During the last 24 hours of peritoneal irrigation our solution contained 50 mg. per cent of sodium sulfadiazine and a blood level of 5.9 mg. per cent was obtained. A sulfadiazine level of 10 to 20 mg. per cent in irrigation solution would be more effective than penicillin as a prophylaxis against the gram-negative bacilli, the most likely contaminants, since these are in general more sensitive to sulfadiazine. The inclusion of both sulfadiazine and penicillin in the fluid would be ideal. We believe that streptomycin should be kept in reserve for vigorous treatment if peritonitis develops in spite of the above precautions. The use of low levels of this antibiotic in the irrigation solution prophylactically would be liable to lead to the development of streptomycin resistant organisms.

The fact that our patient had amenorrhea and developed temporary generalized hirsutism following peritoneal irrigation makes it seem quite possible that, with the dialysis of solutes there was also a transferral of hormones from the plasma and interstitial fluids to the irrigating solution. Abbott and Shea [30] postulated this possibility. As was noted above, our patient is now

* These drains are usually constructed so that there is an open space between the perforated casing and the suction tip. This opening increases the chances of contamination because fluid can escape into the dressings unless continuous suction is applied. By using a screw cap to eliminate this space, a closed system is established and peritoneal drainage occurs as intra-abdominal pressure is increased.

having regular normal menses and, when last seen, the hirsutism was rapidly disappearing. This question should be investigated further.

The development of hypertension in our patient was to us a very interesting phenomenon. To our knowledge, this complication has not been encountered previously in experimental or clinical mercury poisoning. Although BAL may produce hypertension, this occurs within 30 minutes following an injection and rapidly disappears.[33, 34] The marked hypertension in our patient developed four days after BAL was discontinued. It, therefore, seems probable that this complication occurred as a result of the severe renal damage and that it has not been observed previously in mercury poisoning because patients with such a degree of renal damage have not lived long enough for this complication to develop. Edwards [35] made a very interesting observation in connection with this speculation. In studying the effects on the tubules of lethal amounts of mercury injected intravenously into animals, he found that the kidney of two of his rabbits, in addition to tubular damage, showed marked glomerular damage with enlarged capsular spaces and an occlusive constriction of the neck of the tubules. These two particular rabbits had lived for three to four months after mercury poisoning. The other animals, including rabbits, guinea pigs and rats, lived only 1 to 15 days and did not show such occlusions. He pointed out that "it is possible that a like occlusion would have occurred in the kidneys of most of these animals if they had lived long enough after the bichloride of mercury was injected."

It is difficult to evaluate the importance of BAL therapy in this patient. The fact that mercury was recovered from the colon contents in appreciable amounts on the sixteenth and seventeenth days makes it seem likely that BAL was still being effective in mobilizing mercury and in preventing further injury by mercury being excreted.

A Suggested Therapeutic Plan

In view of recent developments, it seems likely that the mortality in acute mercury poisoning can be greatly reduced.

For the treatment of acute mercury poisoning the following plan would seem desirable.

1. BAL should be administered immediately, preferably in the emergency room or home, to patients who are suspected of having ingested bichloride of mercury. The initial injection should be 3.5 to 4.5 mg.* per kilo of body weight followed in two hours by 2 to 3 mg. per kilo and at intervals of six hours by four additional doses of 2 to 3 mg. per kilo. Thereafter one should administer 2 to 3 mg. per kilo twice daily until all evidence of poisoning has disappeared.

2. Gastric lavage should be carried out immediately and thoroughly. Four per cent sodium bicarbonate solution, always easily available, is prob-

*The large per kilogram dose should be used in small individuals and young children may require even greater doses.

ably as effective as any other solution in the removal of excess mercury. Colonic flushings should be done approximately twice daily.

3. Every effort should be made in early severe cases to prevent shock. This requires the administration of whole blood, plasma, and crystalloid solutions.

4. Every effort should be made to maintain the fluid and electrolyte balance and to prevent dehydration or edema. Frequent determinations of blood nonprotein nitrogen, plasma CO_2 combining power, plasma proteins, plasma chloride, and hemoglobin are necessary in adjusting the regime.

5. In patients who are anuric, peritoneal irrigation may effectively remove metabolic wastes until renal function returns. The time at which this procedure should be started depends entirely on the condition of the patient and each case should be judged separately. It is never indicated unless the prognosis is otherwise considered to be extremely grave.†

Summary

1. The evolution of the treatment for acute mercury poisoning is discussed.

2. A patient with severe mercury poisoning treated with BAL and whose prolonged anuria was combated successfully by peritoneal irrigation is reported. These therapeutic measures are discussed in detail.

3. An outline for the treatment of acute mercury poisoning is proposed.

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† Peritoneal irrigation is also indicated in the treatment of other acute reversible anuric states.

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ELECTROCARDIOGRAPHIC CHANGES IN DIPHTHERIA *

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THE free use of the electrocardiogram in military hospitals and an epidemic of diphtheria among unimmunized troops presented an opportunity for a reëvaluation of the non-specific electrocardiographic changes occurring in diphtheritic infections.

During combat, diphtheria was not a serious problem among the United States Forces, European Theater. Following the surrender of Germany in May 1945 and the closer concomitant contact of troops with the indigenous population, the incidence of the disease increased rapidly and reached epidemic proportions in the first five months of 1946. The incidence of diphtheria among troops of the United States Forces, European Theater and in the civilian populations of Germany and France is shown in figure 1.[1]

In 1944 there were only 248 cases of diphtheria among the United States Army troops in the European Theater. During 1945 there were 2153 cases and in 1946 there were 1604 reported cases. However, the case rate reached a peak in 1946 since the Theater troop strength was much smaller.[1]

All reported cases were confirmed bacteriologically. In the last six months of 1946, of 432 strains typed at the Theater medical laboratory, 55.3 per cent were of the mitis strain, 42.6 per cent of the gravis strain and 2.1 per cent of the intermedius strain.[1] Of the gravis strains, 97 per cent proved virulent as did 86 per cent of the mitis strains and 68 per cent of the intermedius strains.[1]

In a 1,000 bed general hospital in the American Occupied Zone of Germany, 600 patients with diphtheria were seen in the 15 month period from September 1945 to December 1946. This number included 26 cases of cutaneous diphtheria. The patients were male American soldiers with the exception of 37 drawn variously from female American military personnel, allied military personnel and civilian employees of the War Department. The youngest patient was 18 years old, the oldest 43, and the average age was 23.4 years.

The portable "Cardiette" was the only instrument employed. All tracings were standardized with a deflection of 1 cm. representing 1 millivolt of potential. A tracing consisted of the three limb leads and the precordial Lead CF_5. Leads from other precordial points were not taken routinely.

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An electrocardiogram was recorded as soon as diphtheria was suspected clinically or when a positive culture was reported. Thereafter electrocardiograms were recorded at weekly intervals or more often when indicated. Patients were restricted to bed until two normal electrocardiograms had been recorded after which they were permitted ambulation if afebrile and asymp-

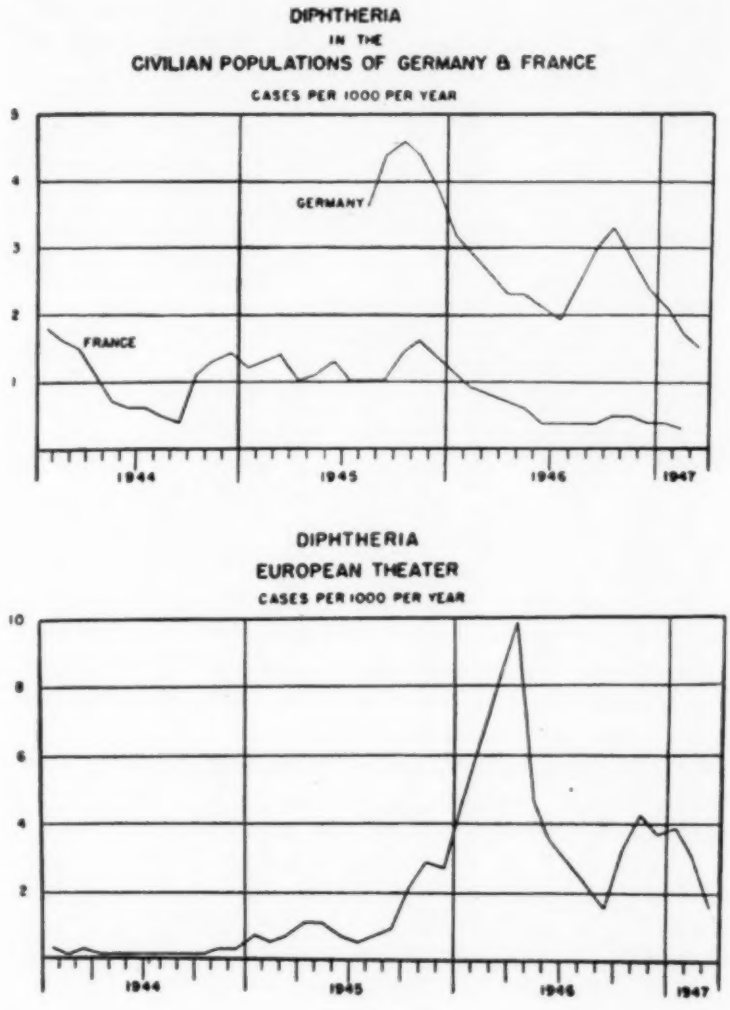

FIG. 1.

tomatic. An electrocardiogram was recorded the day before discharge. Patients were hospitalized for a minimum of five weeks. The criteria of cure were absence of symptoms and evidence of infection, three consecutive negative nose and throat (or cutaneous ulcer) cultures and an electrocardiogram within normal limits. American military personnel with severe or

prolonged electrocardiographic changes were invariably returned to the United States for convalescence. The period of observation for patients with electrocardiographic changes varied between eight and 23 weeks.

Of the 600 cases of diphtheria studied, 143 (23.9 per cent) presented electrocardiographic changes at some time during hospitalization. All electrocardiograms were read by one of two persons and independent interpretation of the same tracing revealed a high degree of correlation.

The electrocardiographic abnormalities noted are presented in table 1:

TABLE I

ECG Abnormalities Noted in Routine Study of 600 Cases of Diphtheria

Abnormality	Number of Cases
A. Low or negative T in two or more leads	108
B. Depressed ST segments in two or more leads	10
C. Prolonged PR interval	11
D. Sinus bradycardia	8
E. Sinus tachycardia	5
F. Numerous ventricular premature beats	4
G. Decreased voltage of QRS in all leads	3
H. Prolonged QT	2
I. Bundle branch block (right)	2
J. Complete heart block	2
K. Wandering pacemaker	1
L. Temporary right axis shift	1
M. Temporary left axis shift	1

From table 1 it can be seen that the greatest number of abnormalities involved the T-waves and ST segments. Liberal standards of T-wave normality were adopted in view of the electrocardiographic findings in the study of a large number of presumably healthy aviation cadets.[2]

ST segment depressions were considered abnormal when they exceeded 1 mm. Abnormal ST segment depressions always occurred in two or more leads and corresponded to the ST segment depressions reported by Ball.[3] This change is illustrated in figures 2 and 3.

An isoelectric T_1 was considered abnormal only if in the series T_1 was at any time 2.0 mm. in height. T_2 was judged to be abnormal if it was less than 2.0 mm. in height with concomitant upright T_1 and isoelectric or upright T_3. In the presence of isoelectric T_1 and isoelectric or negative T_3, T_2 was considered abnormal only if isoelectric or negative. T_3 was regarded as normal unless it was initially upright and became diphasic or inverted. TCF_5 was considered abnormal only if it became negative at some time during the period of observation. Twelve patients were noted to have persistent diphasic or inverted TCF_5 with a normal ST segment as the only electrocardiographic finding; these were not considered significant. To avoid error, a tracing with T-wave abnormalities was considered significant only if T-wave changes were present in two or more leads. T-waves were not reported as abnormal because of the arbitrary standards of low voltage unless they had lost their characteristic configuration and had become broad and rounded. No cases with borderline tracings have been included; one

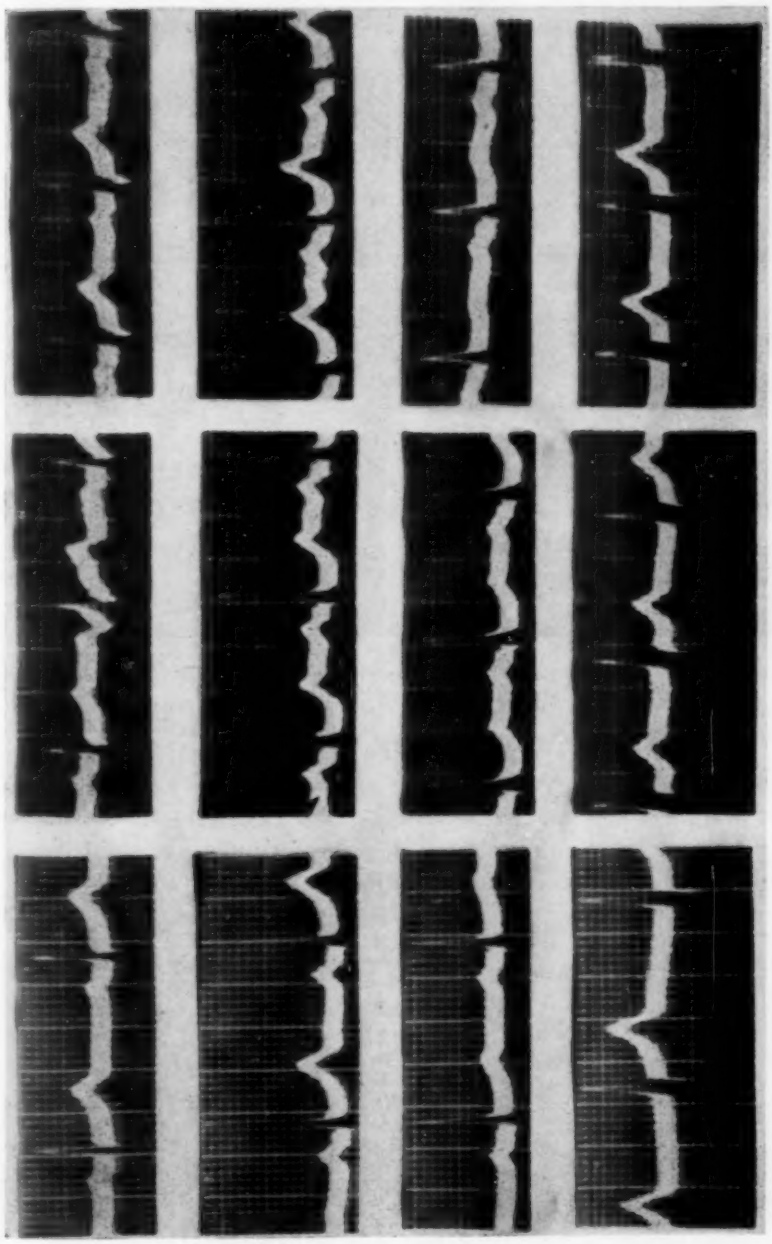

FIG. 2. Low origin and "saucering" of ST segment not yet present in the second week of illness, present in the third week and has disappeared in the fourth week.

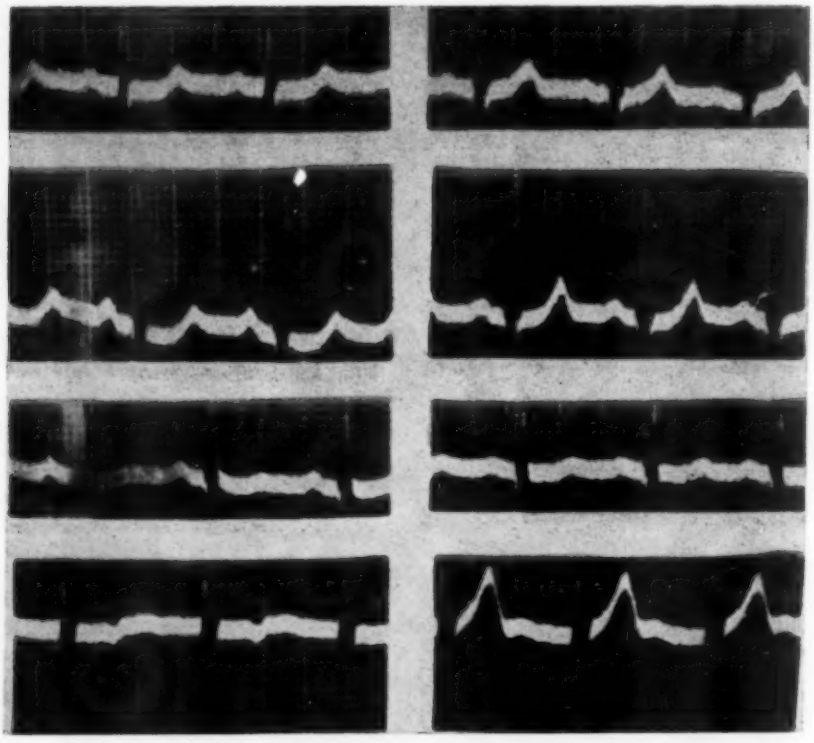

FIG. 3. Low origin and "saucering" of ST segment in the second week; no longer present in the fourth week.

or more of these tracings was invariably preceded by indisputably normal or frankly abnormal tracings. Some of the T-wave changes noted are presented in figures 4 through 7.

Table 2 shows the combination of T-waves affected, the total number in each combination and the average duration in weeks.

TABLE II

T-Wave Changes (Flattening to Complete Inversion)

T-Waves Involved	Number	Average Duration in Weeks
$T_{1,2}$	2	3.0
$T_{1,3}$	8	3.5
$T_{1,4}$	5	4.5
$T_{2,3}$	30	4.0
$T_{2,4}$	4	2.5
$T_{1,2,3}$	25	5.5
$T_{1,3,4}$	6	4.5
$T_{1,2,3,4}$	28	7.5
	108	4.3

T-wave abnormalities were noted most frequently in the limb leads and represented diffuse myocardial involvement. Abnormalities generally per-

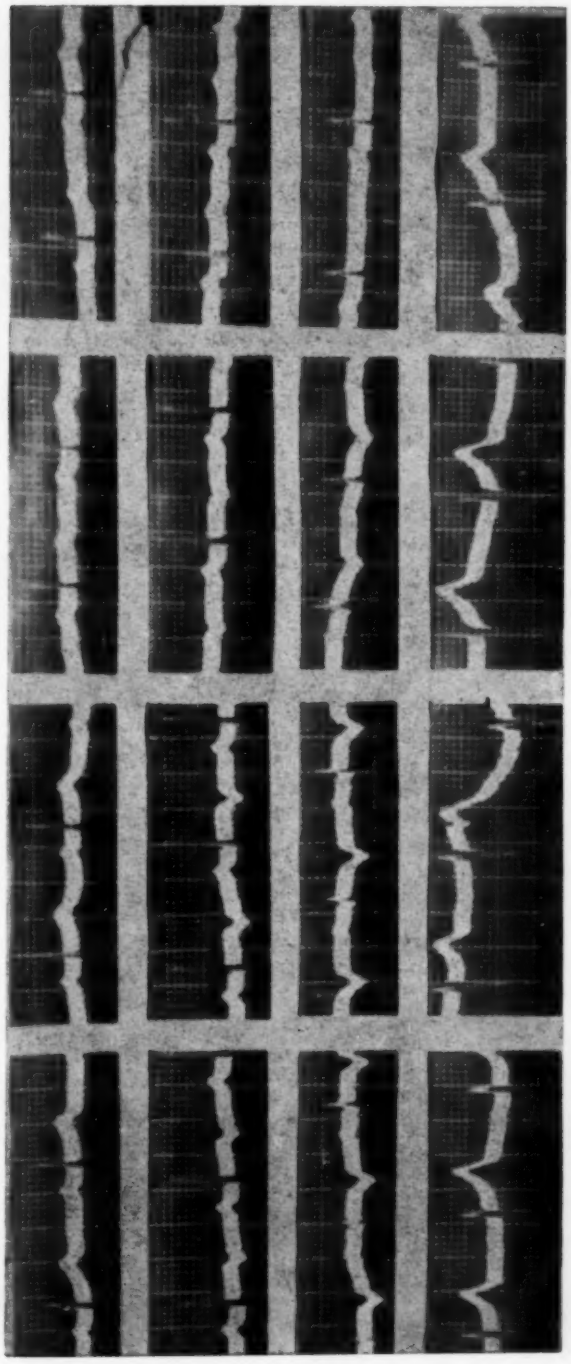

FIG. 4. Inversion of T_2 and T_3 in the second, third and fourth weeks of illness. T-waves in all leads are normal in the fifth week.

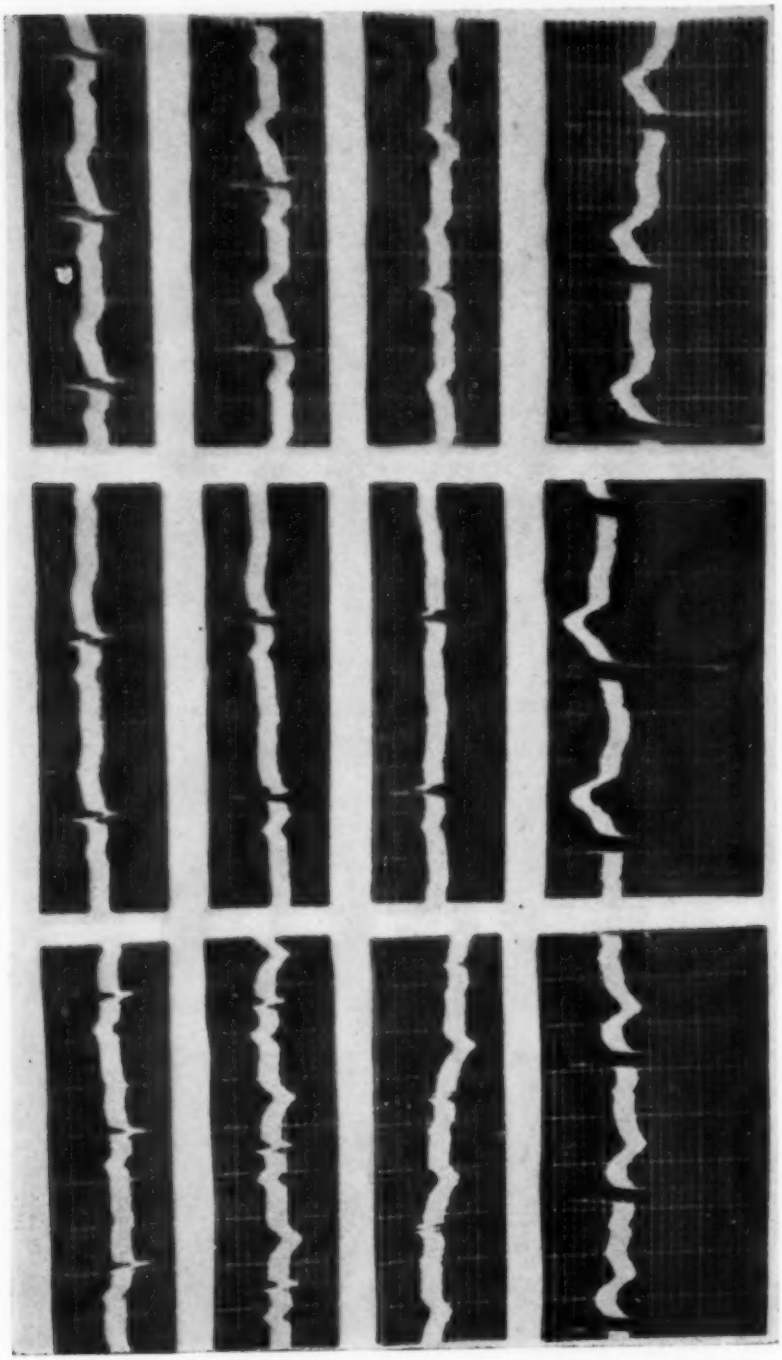

FIG. 5. Inverted T-wave in all leads and marked decrease in amplitude of QRS. Tracings shown are in the second, seventh and thirteenth weeks of illness.

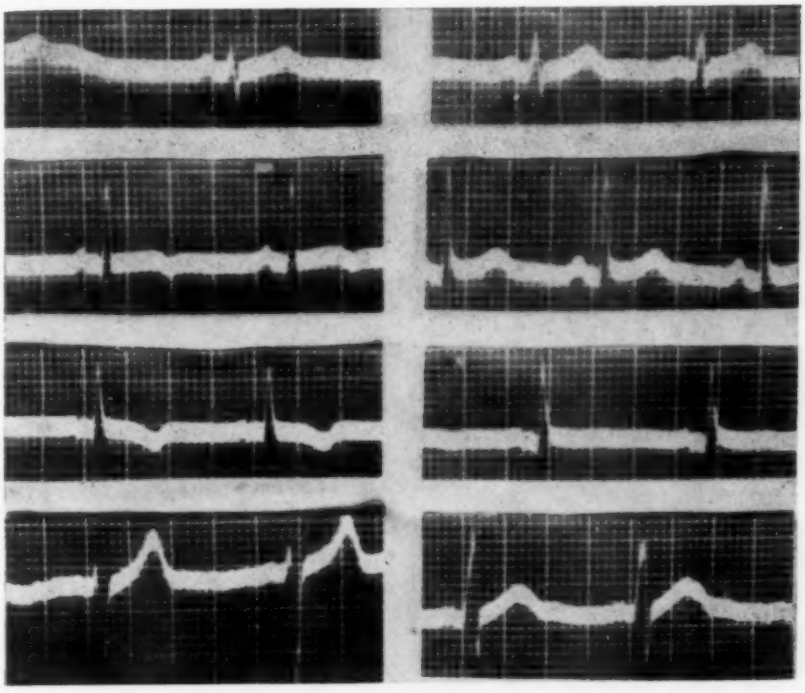

FIG. 6. Inversion of T_2 and T_3 occurring in the second week and returning to normal configuration in the fourth week.

sisted directly in proportion to the number of leads involved—this is well borne out by the 7.5 week average duration of abnormalities present in all four leads. T-wave abnormalities persisted for from two to longer than 23 weeks. Patients with persistent abnormalities in all leads usually had manifested clinically severe infections.

QRS complex changes were infrequent. Slight slurring and splintering were common but the only significant prolongation occurred in the two patients with right bundle branch block. Low voltage QRS in all leads occurred in three cases and accompanied low voltage T-waves.

Prolonged QT was observed twice and did not persist. One patient showing this change had a moderately severe pharyngeal diphtheria, no other electrocardiographic changes, but an acute anxiety reaction with hyperventilation.

Sinus bradycardia (rate less than 50 in the absence of heart block) was observed in eight patients who eventually had stable rates between 70 and 80. The slowest rate recorded was 42. Sinus tachycardia (rates of 130 or more and disproportionate to fever) occurred in five patients.

The upper limit of normal for the PR interval was considered to be 0.22 sec. and this was regarded as abnormal if the PR interval in any electrocardiogram of a series was less than 0.20 sec. (with rate considered). Pro-

FIG. 5. Inverted T-wave in all leads and marked decrease in amplitude of QRS. Tracings shown are in the second, seventh and thirteenth weeks of illness.

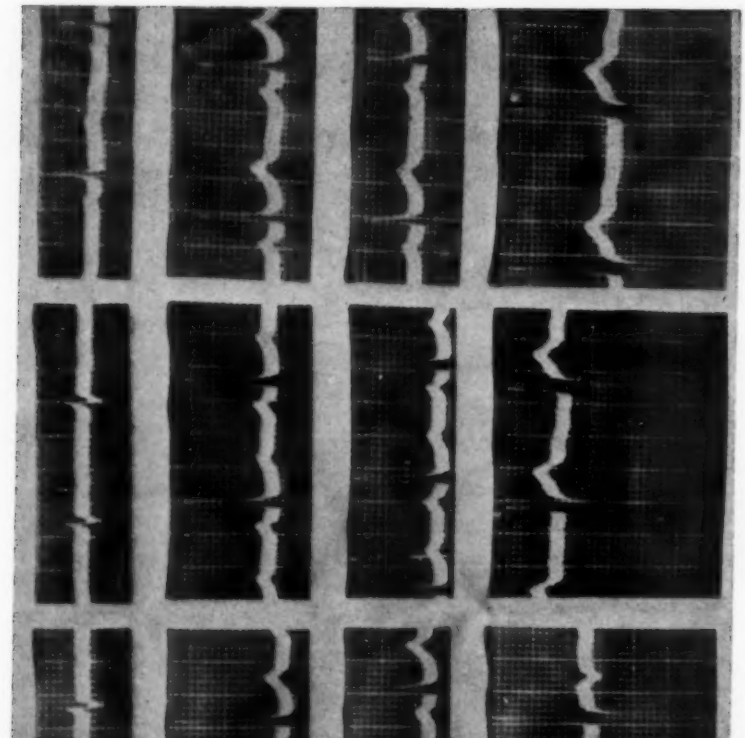

FIG. 7. T-wave changes in Leads I, II and IV and temporary right axis shift. Tracings shown are in the third, sixth, seventh and eleventh weeks of illness.

longation of the PR interval occurred in 11 patients (excluding two with complete A–V block). The commonly held opinion that prolongation of the PR interval is the most common abnormality in diphtheritic infections was not substantiated by this study.

The two patients with complete heart block had remarkably parallel courses. Each had a previous admission because of exudative tonsillitis, one with a small peritonsillar abscess. Beta hemolytic streptococcus was cultured from the throat of each and a gratifying response was obtained with sulfadiazine in one case and intramuscular penicillin in the other. They were both returned to duty within the week, completely asymptomatic. One patient was returned to the hospital after six days, the other after eight because of weakness and syncope. Upon admission, each was in cardiovascular collapse. Complete heart block was diagnosed clinically and substantiated by the electrocardiogram. *Corynebacterium diphtheriae* (*gravis*, virulent) was cultured from the pharynx of both patients. The electrocardiogram of one patient was normal after six weeks, that of the other after 10 weeks. Following subsidence of the complete block, the only abnormality was prolongation of the PR interval (maximum 0.44 sec.). Recovery was uneventful.

Right bundle branch block in two patients persisted for three and five days after which there was deep inversion of all T-waves. The electrocardiogram was not within normal limits after 18 weeks in one patient nor after 23 weeks in the other.

Of the 26 patients with cutaneous diphtheria, four had electrocardiographic abnormalities. One patient with a single 3 by 4 cm. ulcer on the lower leg had negative T-waves in all leads and eventually a severe generalized polyneuropathy.

Two deaths occurred in the series of 600 patients. Neither patient had bundle branch block at any time but both had negative T-waves in all leads. A photomicrograph of the myocardium is presented in figure 8.

Although realizing that statistical generalities may not be applied to individual cases, the study of these 600 patients permits the general observation that if a patient with diphtheria has not shown electrocardiographic changes by the end of the fourth week after the onset of his clinical infection, the possibilities of myocardial involvement from the disease are few. Only five patients presented their first electrocardiographic changes after the fourth week, three in the fifth week, one in the sixth week and one in the seventh week. One hundred twenty-one of the 600 patients were seen after the twentieth week following return to duty and all had normal electrocardiograms.

The electrocardiogram in diphtheria can occasionally be palindromic—abnormal at one time, normal several weeks later and abnormal again in a week or two. This phenomenon was observed four times in the series and in each instance the abnormality was negative T-waves. In one patient the

electrocardiogram alternated between normal and abnormal for eight weeks. No correlation could be established with persistence of the carrier state.

No correlation was possible between the severity of the infection and the severity of the electrocardiographic changes. The patients with the most marked and prolonged abnormalities usually had clinically severe infections

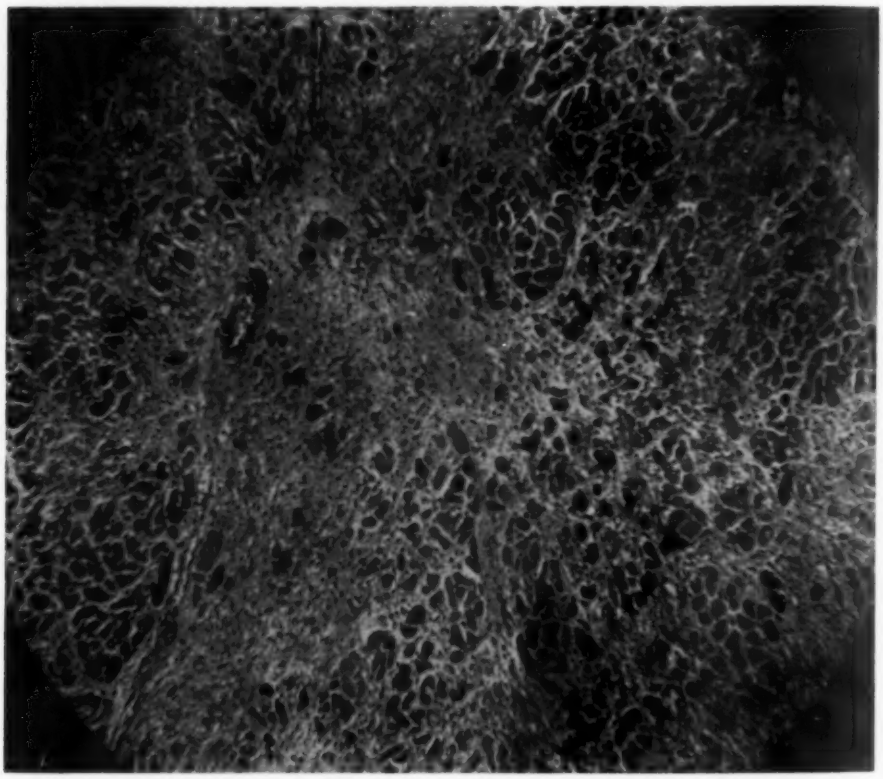

FIG. 8. Myocardial degeneration in a fatal case of diphtheria.

but some patients with mild infections who were asymptomatic after the first few days had marked and persistent electrocardiographic changes.

The presence of the most common abnormality, T-wave changes, could not be predicted by evaluation of the pulse, blood pressure determinations or auscultation of the heart.

SUMMARY

1. The electrocardiographic study of 600 consecutive cases of diphtheria is reported.

2. Significant electrocardiographic abnormalities were found in 143 cases (23.9 per cent).

3. The most frequent change was decreased voltage or negativity of the T-waves. The belief that PR prolongation is the most common finding in diphtheria was not substantiated.

4. Phasic alternation between normal and abnormal electrocardiograms in diphtheria was noted.

5. Severity of clinical infection and severity and duration of electrocardiographic changes in diphtheria cannot be correlated.

6. The electrocardiogram is essential in the evaluation of the physical state of patients with clinical diphtheria both in the acute and in the convalescent periods.

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BOECK'S SARCOID: OBSERVATIONS ON SEVEN PATIENTS, ONE AUTOPSY *

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SEVEN patients with Boeck's sarcoid have come under our observation in a large Naval Hospital during the past 18 months. One died suddenly, permitting more complete study of the disease process. The circumstances surrounding the clinical course and final recognition of the disease in these patients have aroused our interest. We would like to transmit that interest to others, for we are certain that the disease is not uncommon and is, at present, resting uneasily under other diagnostic titles. Our postmortem observations in this one case of sudden death are of value and will be given in detail.

Boeck's sarcoid is not a rare disease. Many excellent clinical and pathological studies of it have been published. Its varied clinical features and its histological picture are well known, though its fundamental nature is not understood. It can usually be identified with certainty.

The infrequent recognition of this disease can be readily explained. Few physicians have made its acquaintance; nor is this remarkable. Only recently has it been realized that sarcoid may affect in its mild chronic relapsing course every organ in the body. At any one time only limited symptoms or signs may be present which go unrecognized as being a part of this disease picture, or more frequently, are mislabelled another disease. This reflects both the slow development of knowledge of Boeck's sarcoid, and its confusing clinical manfestations. An excellent historical summary and clinical review is to be found in the Frank Billings lecture of 1941 by Longcope.[1]

We shall present in tabular form the pertinent clinical facts of these seven patients. They illustrate how and under what circumstances the disease sarcoid may appear in clinical practice. Some observations are offered from this experience which may prove helpful in the recognition and the management of patients with this affliction.

In table 1, we note that these patients were young adults and that four of the seven were Negroes. This is in accord with common experience. Except in one instance, there had been intermittent symptoms for from four days to 10 months. The symptoms themselves showed no consistency, either alone or in combination, and served rather to suggest more common diseases as reference to the admitting diagnoses in table 3 makes evident. Similarly, the physical findings on admission to the sick list were no more than just consistent with the presenting symptoms, with one exception. The peculiar skin lesions seen in the first patient may have been distinctive

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of Boeck's sarcoid. No skin biopsy was ever taken, and the significance of these lesions was not appreciated until after the patient returned to duty.

Table 2 presents the roentgenographic and the positive laboratory findings. Five of the patients had widened hilar shadows interpreted as evidence of enlarged lymph nodes in this location. In addition, signs of sarcoidosis in the lung parenchyma were observed in patient No. 5. At least, it seems fair so to interpret the development of peribronchial mottling in the chest. We know from histological evidence that this patient had almost universal involvement of voluntary muscle by sarcoidosis, that his disease was progressive during the six months under our observation, and that sarcoid

TABLE I

Case	Age	Sex	Race	Symptoms and Duration of Onset	Physical Findings on Admission
1	27	M	W	2 months—Weakness, pain in the head and neck, loss of weight, skin blemishes, swelling of glands in the groin.	Inguinal and axillary adenopathy. On arms and neck were raised blanched skin lesions 5–10 mm. in diameter.
2	22	M	W	10 months—Recurrent episodes of abdominal pain, nausea, vomiting, fever, and fleeting joint pains.	Generalized lymphadenopathy, pallor, fever, weight loss of 40 pounds, pulse rate of 100.
3	20	M	B	6 weeks—Swelling of the glands in the left side of the neck, slight fever.	Generalized lymphadenopathy, slight fever, swelling of the left arm.
4	26	M	W	4 months—Migrating joint pains following scarlet fever.	Fever, tender knee joints.
5	20	M	B	4 days—Pain in forearms, wrists, between the shoulders, bilateral parotid swelling.	Not remarkable except for fever, pulse rate 90 to 110.
6	27	M	B	0 days—No symptoms. Suspicious shadows on routine chest X-ray.	Not remarkable.
7	31	M	B	2 months—Anorexia, weakness, loss of weight, pain in the calves of the legs.	Generalized muscular atrophy. Pulse rate 90 to 100.

lesions are frequently found to be present in the lungs. Certain it is that enlarged mediastinal lymph nodes, as indicated by widened hilar shadows on the roentgenogram, are an important and early feature of this disease.

The laboratory procedures performed in each patient reflected in general the physician's desire to find a satisfactory diagnosis. It is not surprising that tuberculosis took first place in the differential diagnosis in view of the frequency of widened hilar shadows in the roentgenograms, low grade fever, weakness, and elevated sedimentation rate. In all patients acid fast bacilli were searched for in sputa and gastric washings without success. In one patient a tuberculin test was not done. In six it was negative, but in one of these, patient No. 5, it changed to positive on the fourth test, eight months

after the onset of sarcoidosis and while the disease was still active clinically. No other evidence of tuberculosis has yet made its appearance in this man.

The blood picture presented by these patients was not remarkable, even on repeated examination. In four, an elevated leukocyte count was present at some stage of the disease, though the differential was never abnormal. Eosinophilia appeared but once, in one patient, and was not confirmed by subsequent study. The serum protein in two patients was found to be elevated and in both the globulin fraction was above normal. Unfortunately, this feature was not looked for in the other five. The sedimentation rate was above normal in five patients upon their admission to this hospital and

TABLE II

Case	X-Ray Findings	Positive Laboratory Data
1	Chest—Repeated films showed hilar shadows, lung markings and parenchyma to be within normal limits.	SR up to 65. Lymph node biopsy—sarcoid.
2	Chest—Heart normal in size, lungs clear, and no evidence of mediastinal abnormality.	SR up to 52. Two lymph node biopsies—sarcoid.
3	Chest—Bilateral hilar adenopathy. Lung parenchyma clear.	One lymph node biopsy elsewhere—"possible tuberculosis." Similar biopsy here—sarcoid.
4	Widened hilar shadows with marked peribronchial infiltration in the right hilus. 8 months later the hilar shadows were normal.	SR up to 60. Two lymph node biopsies equivocal; the third was definitely sarcoid.
5	Accentuation lung markings throughout, particularly both hila. Later peribronchial parenchymal mottling.	SR up to 28. Early negative tuberculin tests became positive. Elevated serum protein due to hyperglobulinemia. Lymph node and muscle nodule biopsies—sarcoid.
6	Enlarged peritracheal hilar node on right, enlarged left hilar shadow. Later, further widening of the hilar shadows.	SR up to 15. Two lymph node biopsies—sarcoid.
7	Bilateral enlargement of hilar nodes.	SR up to 23. Elevated serum protein due to hyperglobulinemia. Lymph node biopsy—sarcoid.

remained so for varying periods of time thereafter. In the third patient a determination was never made, and in the sixth it was never above 15. Neither of these patients had fever while in the hospital. In one, the first, the rate became normal just before discharge, though he never had fever. In two patients (patients 2 and 4) the sedimentation rate became normal before the disappearance of fever. In two others (patients 5 and 7) it remained elevated until the time of disposition, though both had been without fever for three months preceding. It may be of significance that in these latter two instances the disease was manifestly progressive throughout our study.

From a diagnostic standpoint, the laboratory procedures were of greatest aid in excluding disease for which specific tests are available. An elevated serum protein with hyperglobulinemia may well prove to be a constant feature, but our experience is only suggestive. In the light of present knowledge, the final diagnosis must be made, and can usually be made with assurance, by histological study of a biopsy specimen. In all of our cases an enlarged lymph node was the specimen removed. In one instance, four successive biopsies in nine months were required before the characteristic histological lesion was found, and in another a biceps muscle nodule provided the diagnosis we sought. However, a later lymph node biopsy in this patient did show sarcoid. In patient 5 lymphadenopathy was not conspicuous, but when it was finally appreciated that his chronic corneal lesions had first

TABLE III

Case	Admission Diagnosis	Subsequent Diagnoses				Disposition
1	April 22, '44 Chronic lymphadenitis				May 1, '44 Boeck's sarcoid	Nov. '44 Civil life
2	April 27, '44 Medical observation	May 4, '44 Rheumatic fever			July 11, '44 Boeck's sarcoid	Sept. 44 Civil life
3	May 4, '44 Lymphadenopathy	June 1, '44 Tuberculosis, lymph node			Aug. 17, '44 Boeck's sarcoid	Sept. '44 Civil life
4	April 10, '44 Rheumatic fever				March 22, '45 Boeck's sarcoid	Mar. '45 Civil life
5	May 3, '45 Catarrhal fever	May 4, '45 Mumps	May 4, '45 Catarrhal fever	July 8, '45 Active pulmonary tuberculosis	Nov. 2, '45 Boeck's sarcoid	Mar. '46 Transferred to VAF
6	February 12, '45 Medical observation	February 12, '45 Possible Hodgkin's disease	July 9, '45 Active pulmonary tuberculosis		Nov. 16, '45 Boeck's sarcoid	Dec. '45 Civil life
7	April 9, '45 Pseudohypertrophic muscular dystrophy	May '45 Progressive muscular dystrophy	July 5, '45 Active pulmonary tuberculosis		Nov. 23, '45 Boeck's sarcoid	Dec. 12, '45 Death

appeared in association with a bilateral parotitis (uveoparotid fever of Heerfordt) an epitrochlear node was found, removed, and proved to contain the lesion of sarcoidosis. Lymph node biopsy is necessary and usually accurate in the diagnosis of this disease. One should exhibit no more hesitancy in its use, even in repetition, than one does in making repeated studies on the blood in cases of diagnostic confusion.

Table 3 summarizes the diagnoses suggested. Through the diagnoses recorded in the course of the patient's illness one can visualize the clinical picture confronting the physician, and to some extent the clinical progress of the disease.

Five patients were discharged in the belief that the disease had become inactive. It is generally accepted that many spontaneous cures occur, even

after one or more relapses. Patient 5 was transferred to a Veteran's Hospital for continued observation because of signs of progression, in the absence of symptoms. The abbreviated data of the tables do not quite tell the story. One of his earliest symptoms was parotid swelling, diagnosed as mumps, which subsided promptly. His presenting symptom for the following six months was a migrating muscle soreness, which came to involve all voluntary muscles. Coincidentally, one could find in every palpable muscle innumerable small firm nodules, not unlike capsules, such as are used in oral medication. There was continuous fever and an elevated sedimentation rate. After six months fever and muscle soreness ceased but three other features now became prominent, in spite of the fact that the patient felt greatly improved. Both parotids became persistently enlarged and firm; a bilateral iritis appeared, with involvement of the posterior surfaces of each cornea. Roentgenograms of the chest revealed a peribronchial mottling within the lung parenchyma. Obviously the disease was active and progressive in spite of the patient's improved well-being. The sedimentation rate continued to be elevated until the date of transfer. One is inclined to believe that this patient will eventually succumb to his disease, even as patient 7. Both of these patients had widespread lesions of sarcoidosis, and both continued to have elevated sedimentation rates throughout the period of observation. In four patients the sedimentation rate became normal when the clinical signs of activity ceased. This suggests that an increased sedimentation rate may be an accurate measure of the activity of this disease.

The record of patient 7 will be presented in detail. The clinical story is interesting though not unique in the annals of recorded cases of Boeck's sarcoid. His sudden and unexpected death is sufficiently rare to warrant recording in its own right.

A negro, age 31, was first admitted to the sick list on April 9, 1945, with a diagnosis suggested as pseudo-hypertrophic muscular dystrophy, and complaining of anorexia, weakness, and pain in the calves of the legs for two months. He had previously been well. The pain had been throbbing in character, and there was associated numbness in the hands and feet. Examination was not remarkable save for evidence of weight loss of 16 pounds, and a generalized muscular atrophy. In May the diagnosis was changed to progressive muscular dystrophy. At this time he developed an acute swelling of both parotid glands. A roentgenogram disclosed no salivary calculi. This swelling subsided within three weeks, but during its course a bilateral iritis made its appearance, to become chronic in both eyes. The leukocytes numbered 5600 with a normal differential; the sedimentation rate was 6, the tuberculin skin test was negative in two strengths, and there were no acid fast bacilli in the sputum. Chest roentgenogram showed bilateral enlargement of the hilar nodes, thought to be tuberculous. On this evidence, and in the belief that the iritis might be from the same cause, the diagnosis was changed to active pulmonary tuberculosis and the patient transferred to this hospital. Here the blood cell counts and smears were consistently normal, but the sedimentation rate was found elevated to 20 to 30 upon repeated occasions until death. From July 11 to September 5 there was a daily fever of one degree, but none thereafter. Acid fast bacilli could not be found upon repeated examinations of sputum and gastric washings. Roentgen studies demon-

strated both hilar shadows to be unusually wide, with calcification within them; the left costo-phrenic angle was blunted and thickened pleura extended upward to the left apex along the lateral chest wall. The Mantoux test was negative in both strengths. Bronchoscopy on August 24 gave evidence of extrinsic pressure on the left bronchus. In August the ophthalmologist reported conjunctival injection in each eye and slight pupillary involvement. The slit lamp revealed a few keratitic precipitates on Descemet's membranes and the aqueous clear. The opinion was expressed that these lesions were not tuberculous in origin. In October roentgen therapy was directed to the hilar regions for diagnostic purposes, but no change in the shadows resulted. In November, while reviewing this man's entire record, it suddenly dawned on us that the simultaneous occurrence of parotid swelling and iritis five months earlier probably represented an uveoparotid fever of sarcoidosis. An enlarged epitrochlear node was removed, and the diagnosis of Boeck's sarcoid established on November 23.

FIG. 1. Myocardium of left ventricle invaded by sarcoidosis.

On the same date the plasma protein was found to be elevated, the increase due to a hyperglobulinemia. The ophthalmologist now described the eye lesions as follows: Bilateral circumcorneal injection with infiltration of Descemet's membrane in the right eye. In the left, punctate spots were distributed over the posterior surface of the cornea. Considerable pigmentation of the anterior lens capsule on the right. The patient felt and appeared to us perfectly well, except for the distress of the progressive lesions in the eyes. While making arrangements for travel on Christmas leave, he fell dead in a telephone booth.

Postmortem examination was made four hours after death. The body was that of a well nourished colored male, age 32, weighing 175 pounds. Each pupil measured seven millimeters in diameter. The sclerae were obscured by a hazy gray membrane. The corneal and conjunctival vessels were dilated and there were flame shaped hemorrhages radiating from each pupil. Within the thoracic cavity the visceral pleura was

adherent to the entire chest wall, the diaphragm, and pericardium. The right lung weighed 500 grams. Its pleural surface was studded with raised discrete, bluish nodules, five millimeters in diameter. They appeared to arise in the parenchyma of the lung and project above the surface into the visceral subpleural space. The pulmonary vessels were free of emboli. The lung parenchyma contained the same type of nodules, was air containing, and showed no caseation or cavitation. The left lung weighed 520 grams and was similar in appearance to the right lung. The hilar lymph nodes were greatly enlarged, discrete, and hard. The pericardium and epicardium were grossly normal. A peculiar tumor-like infiltration of the myocardium was evident in the walls of both ventricles, the interventricular septum, papillary muscles, and the base of the aortic valves (figure 2). These infiltrations were circumscribed, irregularly shaped, and pale yellow. The valve leaflets appeared normal, and the coronary arteries were free of occlusive or degenerative changes. Within the aorta

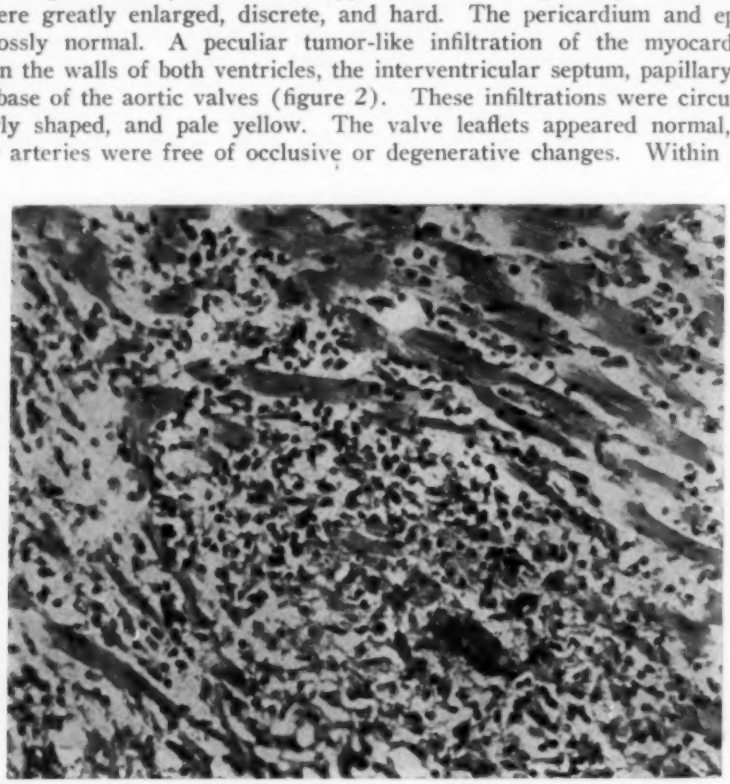

FIG. 2. Myocardium. Earliest lesions are at lower left. Older lesion is in the center.

were a few arteriosclerotic plaques. The spleen weighed 220 grams. The capsule was slightly wrinkled and within the parenchyma were many discrete, oval, gray tubercles. Both kidneys were of normal size and their capsules stripped with ease. No gross changes were noted in the kidneys, ureters, or bladder. The gastrointestinal tract was normal. Enlarged mesenteric lymph glands were present. The liver weighed 1200 grams and appeared normal, as did also the pancreas, adrenals, testicles, prostate, thyroid, and brain. Restrictions did not permit the removal of the eyes or parotid glands.

Microscopic examination of the scattered lesions in the lung parenchyma demonstrated that they were single and confluent masses of epithelioid cells containing many large multinucleated giant cells. There was no evidence of caseation, necrosis, or cavitation. Acid fast staining of the tissues failed to reveal tubercle bacilli. There was no zone of peripheral inflammatory reaction, but rather a concentric zone of collagen about most of these lesions. The giant cells were large and less regular than

those seen in tuberculosis, and many contained inclusion bodies of various types. Examination of the sections from the ventricles, interventricular septum, papillary muscles and epicardium revealed extensive replacement of normal tissue by a diffuse sarcoid infiltration. Most of these lesions were confluent, suggesting an inflammatory invasion of tissue with succeeding fibrosis. Lesions of all ages and types were present. The youngest ones consisted mainly of infiltration between intact and fragmented muscle bundles by epithelioid cells, plasma cells and lymphocytes. The oldest showed destruction and replacement of muscle by fibrosis with bordering collagen formation and a diminution in the number of cellular elements. Numerous large giant cells were seen scattered in irregular fashion throughout the granuloma. Many of these cells had inclusion bodies. The liver had single sarcoid tubercles scattered throughout the parenchyma, situated in the portal triad areas. The kidneys, spleen, tracheobronchial lymph nodes, and voluntary muscles all contained similar sarcoid tubercles, but the mesenteric lymph nodes, adrenals, pancreas, brain, meninges, and bone marrow did not.

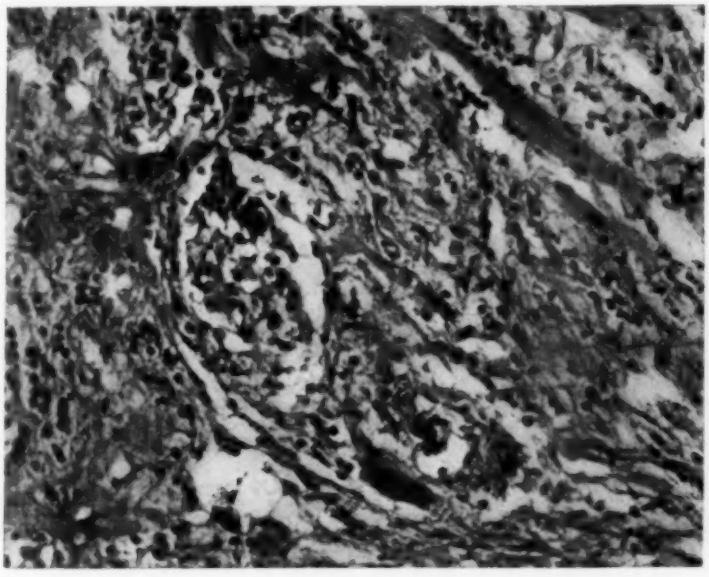

FIG. 3. Myocardium. Older lesions and diffuse fibrosis are shown.

Descriptions of sarcoidosis of the heart made from postmortem observation are rare. Preceding ones have been published by Bernstein,[2] Schaumann,[3] Nickerson,[4] Spencer and Warren,[5] Cotter,[6] Longcope,[1] Johnson and Jason.[7] Before death in this patient there was no suspicion that the heart might be invaded by sarcoid. There were no symptoms to suggest it. The cardiac silhouette was not enlarged. The heart sounds were not thought to be abnormal. No electrocardiographic record was made. However, one sign was present to which more weight should have been given. The patient maintained a pulse rate of 90 to 120, even when afebrile. In reviewing the records of the other six patients in this series, we find the same elevated pulse rate obtained in patients two and five. The former was

dismissed as well. The latter, as previously noted, has a widespread and progressive form of the disease. An ECG tracing made just before his transfer to another hospital showed an elevation of the S–T segment in $CF_{1, 2, \text{ and } 3}$, with inversion of the T_4, particularly marked in CF_1. These changes were interpreted as evidence of invasion of the myocardium by sarcoid. Knowing that the myocardium may become a site of sarcoidosis without producing symptoms and that it may result in unexpected death, one dare not ignore a persistent tachycardia for the warning it may be.

In our patient, there were extensive lesions of all ages and types in the myocardium, including the interventricular septum and the epicardium. The youngest consisted of an infiltration of lymphocytes, plasma cells, and

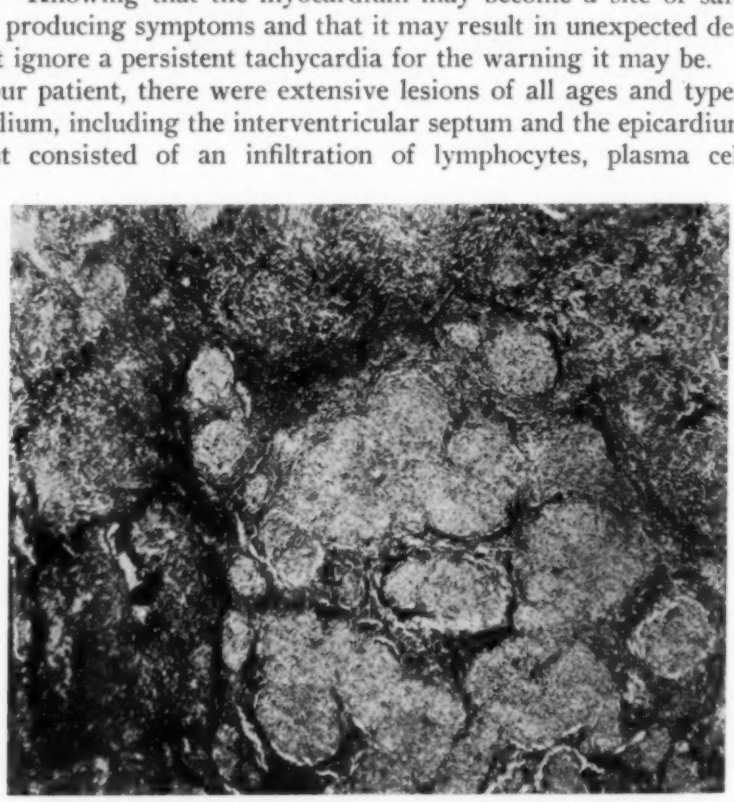

FIG. 4. Lymph node shows classical lesions of sarcoidosis.

macrophages into the myocardium between the muscle bundles. Older lesions showed more of the classical picture associated with sarcoidosis, mainly, a destruction of the myocardium with the site of the muscle bundles occupied by large pale staining mononuclear epithelioid cells and giant cells together with a moderate amount of collagen (figure 2). In the oldest lesions the epithelioid cells were replaced by fibroblasts and fibrocytes with resulting scarring (figure 3). Injection of macerated tissue from this case failed to produce tuberculosis in the guinea pig.

Grossly, the lesion of sarcoidosis appears the same in all organs, except that in the lung it may take on a bluish color from deposition of inhaled carbon pigment. Generally, it appears as a sharply circumscribed, oval or irregularly shaped, gray or yellow mass from one to 25 millimeters in diameter.

It cuts with ease and does not exhibit calcification. It has a hard and fleshy feel, and never shows cavity formation or caseation. Microscopically, the sarcoid tubercle exhibits a characteristic picture which may vary slightly with the age of the lesion, but is sufficiently unique to be recognized quite readily. It consists of masses of large, pale staining epithelioid cells usually surrounded by a concentric zone of collagen fibers. The lesions may be single or confluent and frequently exhibit a mosaic pattern (figure 4). The tubercles are usually devoid of a peripheral inflammatory zone, polymorphonuclear leukocytes are absent, and central necrosis is not seen. The giant cells associated with sarcoidosis are usually larger and more irregular in shape than those seen in tuberculosis, frequently have more nuclei (up to 30)

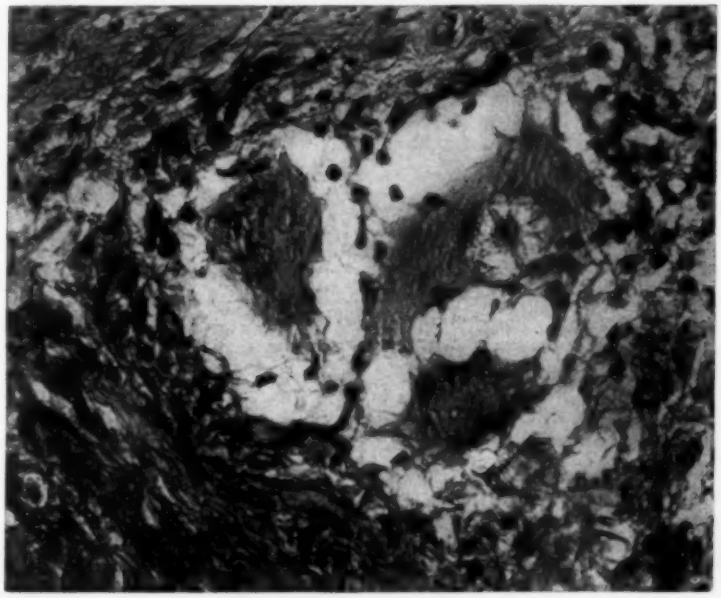

FIG. 5. Asteroid inclusion body in lymph node from patient who had no evidence of sarcoidosis.

and often show inclusion bodies of various sizes and shapes. The Schaumann type of inclusion body is usually seen as an oval shaped mass with concentric laminations, and may show yeast-like budding. This type often appears calcified and at times may reach a size larger than its parent giant cell. Friedman [8] describes asteroid inclusion bodies as large spheres, many of which show sharp pseudopodia protruding from the surface. He believes that different stages in the age of the asteroid body can be differentiated and that the younger forms are those which show a clear or punched-out area resembling a vacuole which often has a tiny pink staining sphere or coccoid body in the center. The diagnostic worth of asteroid inclusion bodies is debatable. The authors have seen asteroid bodies in giant cells in lymph nodes removed

from patients having no clinical, laboratory or histological evidence of sarcoidosis (figure 5). The histological structure of the "hard" tubercle must include reticulum fibers. These are usually present in the center of the sarcoid tubercle, but are absent in the tubercle of tuberculosis.

The criteria for a positive histological diagnosis of sarcoidosis proposed by Nickerson [4] are as follows: (1) Caseation must never be present. (2) Caseating tuberculosis should not be found anywhere in the body. (3) Reticulum fibers should be present in the hard tubercle. (4) Polymorphonuclear leukocytes must not be present. (5) Giant cells must be larger than those seen in caseating tuberculosis, they must contain more nuclei and

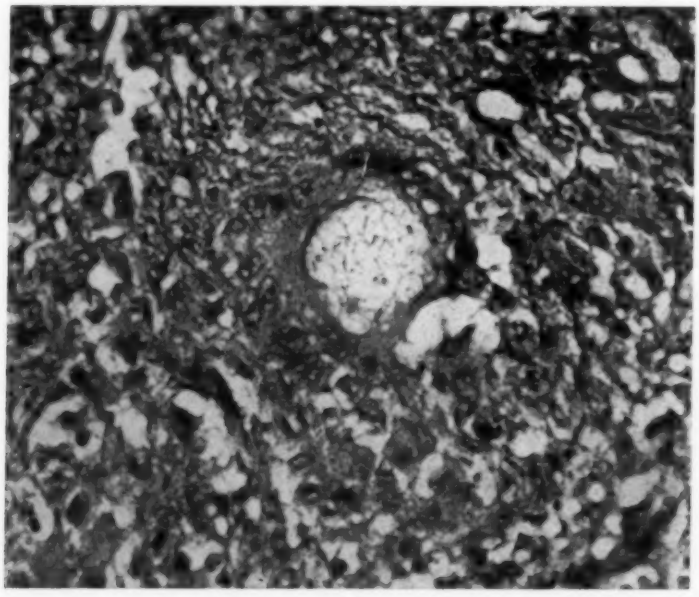

FIG. 6. Sarcoid tubercle of spleen. Giant cell shows vacuoles and coccoid sphere in its center.

the nuclei should be dispersed throughout the cytoplasm.[6] Lesions in the liver should be situated in the portal triad areas rather than mid-zonal, as in caseating tuberculosis. (7) Carbon pigment must not be present in extrapulmonary lesions. To these criteria it is suggested that another be added: One of the various types of giant cell inclusion bodies must be present. This would serve further to protect from confusing the sarcoid tubercle with that of tuberculosis. However, it is felt that these histologic criteria must be combined with the clinical picture of sarcoidosis before one can be absolutely certain of the diagnosis in debatable cases. It is believed that the finding of tuberculosis somewhere in the patient's body does not necessarily rule out the presence of concurrent sarcoidosis.

Our purpose has been simply to call attention once again to this little known, little understood disease, which has been best described as a benign lymphogranuloma. To that end the clinical records of seven patients with Boeck's sarcoid have been briefly reviewed, and the postmortem observation findings in a patient who had an extensive sarcoidosis of the myocardium have been discussed. In conclusion, these comments are set forth:

1. Widened hilar shadows seen in the roentgenogram are a common and early accompaniment of Boeck's sarcoid.

2. An elevated serum protein and hyperglobulinemia may serve to suggest the diagnosis of Boeck's sarcoid.

3. Biopsy provides the only certain method of identification of sarcoid. An accessible lymph node will always eventually provide the necessary specimen.

4. The histological features of sarcoid are definite and usually unmistakable.

5. An elevated sedimentation rate may be an accurate measure of the activity of this disease.

6. A persistent tachycardia should be a warning that the myocardium has been invaded by sarcoidosis.

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CHANGING CONCEPTS OF DISEASE*

By KARL MENNINGER, M.D.,† *Topeka, Kansas*

IN deciding what I as a psychiatrist might present to this representative body of internists, I considered several possibilities. I could talk about something which I understood fairly well but with which you are less familiar, such as the psychodynamics of schizophrenia. This might impress you with my expertness, but it would also probably puzzle you. Or I could talk about something which you know all about and I very little about, and this would amuse you. I could talk about something which we all know about, and this would bore you. So I concluded to talk about something which neither of us know much about, hoping that this might at least intrigue you.

So I begin by assuring you that I am well aware that I know almost nothing about the subject I am presenting except that it is important for us all to think about it.

Perhaps I can enlist your interest in the topic if I recite briefly how I came to begin thinking about it. I have said that I was a psychiatrist. So I was for over 25 years. Recently, however, I have had to become a physician! In my position as director of a graduate school of medical education which includes young surgeons and young internists as well as young psychiatrists; and also in my capacity as director of a sizeable general hospital, I have had to think of medicine as a whole. I have had to try to relate in principle and in practice the functioning of many different kinds of doctors. I have had to revise my comfortable notions about a lot of things which we doctors get into the habit of taking for granted.

For example, I used to think that the accepted formula for any properly trained medical man was very simple—collect data about a patient, organize them, establish a diagnosis, and treat the patient according to the diagnosis. Examination, diagnosis, treatment; patient gets well and lives happily ever after (unless, of course, an error has been made in the diagnosis!)

I am somewhat ashamed to say that it has taken me a quarter of a century to realize that this formula rarely works out this way in actual practice and that it may well be that it is the wrong formula.

What I got out of medical school was the conviction that the world was full of healthy human beings, and that now and then a victim was struck down by a cruel blow from an unheeding Nature—an infestation, a lurking bacterium, a malignant cell. Now and then an inexplicable perversity seized the liver or the pancreas or the bone marrow. As a result, a *"disease"* de-

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veloped and a patient appeared on the doorstep of the physician. With the proper questioning and the proper application of a few indispensable gadgets, the diagnosis was correctly established and the proper treatment instituted.

It never occurred to me in those days to realize that *most* people in the world are sick, and not the exceptional individual who came to the Out Patient Department of the Massachusetts General Hospital. It never occurred to me in those days that the pain produced by a sickness might be experienced by everyone else in the patient's environment more than by him. It never occurred to me to consider how much society determined the illness of a particular individual or how much the individual himself determined, desired, and even inflicted upon himself the suffering for which I as a physician was asked to offer relief. Disease, as I viewed it, and I think I fairly accurately caught the spirit of my preceptors, was an entirely unwanted, useless, purposeless misfortune, acquired inadvertently through an unfortunate concatenation of forces emanating from the best of all possible worlds or from the defective architecture of an hereditary constitution.

It is not often that we discuss the basic philosophical assumptions of medicine, and perhaps most of my audience has been so engrossed, as I have, in doing the daily job with the presenting patient, that we haven't stopped to reflect, as I had to in writing this paper, how much our daily experience has taken us away from such concepts. Don't we all agree, really, that whether we call them psychiatric problems or psychosomatic problems or allergic problems or cardiovascular problems or something else, most of the patients—far and away the majority of patients—that you and I treat day after day cannot be given an accurate, specific, meaningful diagnostic label and do not represent any disease entity?

What shall we call the "disease" represented by a man who has always been frail but has worked very hard to support his widowed mother, did not feel he could afford to get married, buries himself in the details of a complicated job, develops paralyzing headaches, loses time at the office for which pay is deducted from his wages, worries about this so much that he loses sleep and begins vomiting after each meal? Just to make it complicated, he has a leukocytosis and an enlarged spleen. Does not such a case defy diagnosis?

Even in the simplest cases it seems to me misleading to make a diagnosis in the old-fashioned way. A middle-aged puritan spinster appears in my office with a chancre on her lip. Isn't this a simple diagnosis? I don't think so. Nor would you if I told you the circumstances of how she acquired that chancre, whom she acquired it from, how she happened to select that type of man, or why she permitted him to kiss her. Her sickness cannot be accurately diagnosed just as syphilis. She did not come to me because of it. What she came to me for was a more serious thing. She was so depressed about the implications of the infection that she now wanted to kill herself. What is the name of that disease? Is it a part of the syphilis?

The doctor who is giving her penicillin was wise enough to know that penicillin alone would not cure her.

Diagnosis in the sense in which we doctors have used it for many years is not only relatively useless in most cases; it is an inaccurate, misleading, philosophically false predication. Many doctors know this intuitively. When patients ask, "What is this that has gotten me down?" such doctors reply, "Oh, its a respiratory thing," or "Apparently you caught a bug that is going around"; or "You have a cardio-vascular involvement; it's tied up with this worry you have at present. Your blood pressure isn't dangerously high and your heart's making an adjustment to it. I think things will improve when that contract is signed." These are not diagnoses in the old sense; they are evasions of diagnosis. Such doctors might be embarrassed if we pressed them, and I think we have no right to do so because these doctors feel the untruthfulness, the unscientific nature of a diagnosis according to our former schedules. We used to think that a doctor who indulged in such vagueness was an unscientific doctor, that all that was the matter with American medicine was the failure of "the old fellows," as we patronizingly called them, to see the necessity of establishing a diagnosis as a basis for treatment. Of course, there was a certain truth in this, and there was also a certain great falseness in it and it is the falseness that I want to examine today.

I realize that throwing doubt upon the desirability of making a diagnosis as I have done is bound to be disturbing to many physicians. "Granted," they will say, "that one finds many cases in which he cannot make a diagnosis and many in which he has to make a multiple diagnosis, the fact remains that we ought to try to decide what is wrong before we plunge wildly into some kind of therapy. You are attacking a basic foundation stone in scientific medicine. You are encouraging eclecticism and opportunism and shotgun therapy. You are going against everything that we have spent hundreds of years trying to establish."

No, I am not; really I am not. I suffer from the same uneasiness that you do about the consequences of a misinterpretation of what I am saying. But I ask you to listen carefully: *I have not said that* we should not attempt to make a diagnosis. I have merely said that this simple formula of *diagnosis determines treatment* can no longer be carried out as we originally conceived of it, because diagnosis is too complex and attempts to make it simple and definite lead us into error. I have given you some cases to illustrate this and I shall give you some more.

A travelling salesman of 25 had kept at his job for several years in spite of an increasingly extensive exudative and distressing dermatitis. He had had all sorts of treatment for it, to no consistent avail. Because of it he felt unable to make proper social contacts and feeling increasingly excluded from the company of "nice girls" he felt obliged to force his attention upon prostitutes. When even prostitutes were dismayed at his appearance he

convinced himself that his sexual life would have to be a choice between masturbation and rape.

About this time he was inducted into the Navy and after about a year of unsatisfactory service, he was discharged. In his own words, "I guess I just scratched myself out of the Navy." He then proceeded to scratch himself into another hospital, where I saw him.

Everything else having failed, the man was quite willing to see a psychiatrist and proceeded to take advantage of the doctor's invitation to tell him all about his problems. He talked on and on; and the psychiatrist listened on and on. He became intensely emotional in his recollection of the various complications of his life; for the first time the entire pattern began to unroll. The psychiatrist continued to be attentive, permissive, and non-committal.

And now what do you think happened? Having thus relieved himself of guilt feelings, shame, fear and other stored-up emotion, the patient recovered; his dermatitis disappeared? Not so; it promptly became very much worse! Somewhat disturbing to the notion that psychosomatic afflictions can be deftly cured by emotional catharsis, isn't it?

We doctors are all only too painfully aware that our most logical and best intended treatments often make patients worse instead of better. It is a blunder we all make; it derives in part from the fact that we cling to an outmoded practice of making disease-picture diagnoses. This leads to a treatment regime based not on the patient's condition, not on his real disease, but on the preconceptions of the particular person who sees the patient. In the case of the clerk which I related first, the sociologist would make a diagnosis of bad labor conditions, the internist might make a diagnosis of anorexia nervosa, the neurologist might see it as an aggravated migraine. In the case of the young girl, the syphilologist made a diagnosis of syphilis, and the psychiatrist a diagnosis of melancholia. In the skin case just related, five different diagnoses had been made—sexual psychopathy, vocational ineptitude, several kinds of dermatitis, and conversion hysteria.

"Very well," you will say, "perhaps he had all of these; multiple diagnosis is all right. But we must have diagnosis." Yes, but the question is, who is the "we"? Do you mean we internists? we neurologists? we pathologists? we sociologists? we psychologists? we psychiatrists? All of us are interested in the same individual; we all believe in the same scientific laws; we are all studying the same interrelated phenomena. Yet, each of us has our own little list of syndromes and we look for symptoms to fit a preconception without reference to any other "we," and call that a diagnosis. And just as surely as we do that, we violate the basic principle of the modern holistic or totalistic concept of the human organism. In theory there cannot be any such thing as a simple, uncomplicated diagnosis of anything, not even measles. The child with measles has at the same time some educational interruptions, and some social complications, and some disturbed

relationships with parents and siblings. The only scientific right that we doctors have to so label the total situation in which a school child goes home sick with "measles" is the practical usefulness of a term, the full implications of which are fairly familiar to the general public. Any case of measles is far more than measles, any case of syphilis is far more than syphilis, any case of dermatitis is far more than a skin rash.

If, then, there is some practical advantage in adhering to conventional labels, and if in the back of our minds we remember that the total human organism is a physical-chemical-social-psychological interacting unit, what is the harm in continuing to use these convenient medical handles?

In many instances, none—provided we realize that any such diagnosis is a misnomer. But the tendency is to forget this and to assume that sick patients can be treated like automobiles—properly labelled and then passed down an assembly line of specialists for a punch here and a wrench there—without the guiding principle of an overall perspective.

I recall a young banker in a small Wisconsin town who had built up his bank from a hard start by dint of assiduous application and good judgment. He began to suffer increasingly from indigestion and his family physician, who was a member of the Board of Directors of the bank, studied him in the appropriate medical way and made a diagnosis of peptic ulcer. For a matter of eight years dietary and medical treatment kept the pain under control, but as guardian of the health of one of the community's most important citizens his family physician was disturbed by the possibility of hemorrhage, perforation, or chronic invalidism. He had repeatedly urged upon the banker the advisability of surgical treatment. The patient had strenuously resisted. Finally the conscientious doctor insisted upon the operation, and a successful gastrectomy was skilfully performed. He made an uneventful recovery and returned home.

But he did not return to work. He had become depressed. He appeared physically well, but he felt melancholy, pessimistic, unable to take interest in his work, his customers or his friends. Month after month passed and his depression deepened rather than lifted. His very much worried family physician now urged that he go to a sanitarium. To this the patient demurred. Finally under the pressure of friends, family, fellow citizens and doctor, he agreed to go.

While his wife and his physician were making preparations to carry out this plan, the patient committed suicide.

To this day that family physician doesn't understand that tragedy. He keeps wondering what he did wrong. According to our false principles of departmentalized diagnosis and *ad hoc* treatment, he did nothing wrong. The patient had an ulcer and he received appropriate treatment for that; then the patient perversely developed depression and the doctor arranged the appropriate treatment for depression. It never occurred to him that the patient's ulcer was not his disease, depression was not his disease. His dis-

ease was something defective in his total life adjustment. While the bank was struggling he had no physical symptoms, but he had worry; when the bank got on its feet he had no worry, but he developed gastric pain. So long as he had gastric pain, his life adjustment remained in balance. But when this source of suffering was taken away from him he developed another type of suffering and when this final type of suffering was threatened with removal, he killed himself.

What was "the disease" of that banker?

What is the diagnosis in a patient who has coronary symptoms whenever he takes his wife to a party? or in a woman who has migraine on the week ends that her son is home from college?

What kind of arthritis is it which becomes activated with each quarterly meeting of the board of directors?

If a young wife's dysmenorrhea disappears when her husband is drunk, or if a child vomits each morning just before school time, or if an educated young Negro trying to establish himself in a decent business in an average American city develops vascular hypertension at 35, or if the mother of five children who has been working an 18 hour day starts coughing up a little blood, or if a man reared in a home where the drunken father regularly abused his family develops syncope when he goes to his employer's office, or if a rugged individualist who believes in free enterprise exhibits his belief by bullying his employees five days a week and concealing his own feelings of insecurity by week ends of alcoholic anesthesia—if these patients come to see us, as they do every day of the world, what shall we say the disease is, in each case? What are the diagnoses? And what conceivable relationship do any medical diagnostic terms we might apply to them have to the necessary treatment programs?

We cannot make diagnoses to fit such disease pictures as these because our medical diagnostic categories depend upon traditional formulations some of which date back to pre-historic times. Seguin of Peru has, in a recent brilliant article,* called the bacteriological era of medical history the "Golden Age for the demoniac concept of disease, when germs became the scientifically named demons." In giving temporary support to the fallacious causality principle, the discovery of bacteria vastly retarded progress in our scientific medical thinking. Every thoughtful person knows that no thing or event in the world can have *a cause*, and that while the impulse to seek causes is, as Tolstoy says (in *War and Peace*), innate in the soul of man, "the combination of causes of phenomena is beyond the grasp of the human intellect." The early Greek physicians knew this and concentrated not on causes but on the phenomena of disease—the symptoms. Rivaling this "phenomenological concept" were theological concepts which equated disease with sin or with punishment, and then the humoral concepts which later found some representation in endocrinology. Virchow fought against the

* "Concept of disease," Psychosomatic Medicine, 1946, viii, 252–257.

sedes morborum concept of disease which had been crystallized by Morgagni, distinguished by great conflict between the humoralists just mentioned and the "solidists" who sought to locate the "seat of disease" in organs. But in the end Virchow himself fell victim to the very theory he was combatting by locating the seat of disease in the cell.

In common parlance we talk irrationally and childishly about the patient "fighting the disease," "facing it," "resisting it" and the like, forgetting that disease is not something external or alien but it is *of* the patient, and largely his own doing. The real problem is, what forces him to do it so? How have his defenses handled some new situation? And to what extent have those malignant self-destructive tendencies, which are in us all, combined with external forces to result in pain and faltering and sometimes death? It is somewhat shocking to read, even in some modern textbooks of pathology, statements which imply that disease is a *thing*, a horrid, hateful external thing, which invades the human organism like a snake in a dove's nest. Clinical medicine, with the fructifying stimulation of psychiatry and the psychoanalytic study of the unconscious processes, has a far more dynamic and progressive view than a pathology still couched in descriptive phenomenologic and demoniac terms.

For I believe that clinicians have come to think of disease more and more in terms of a disturbance in the total economics of the personality, a temporary overwhelming of the efforts of the organism to maintain a continuous internal and external adaptation to continuously changing relationships, threats, pressures, instinctual needs and reality demands. The concept of biochemical homeostasis of the organism, which Cannon so beautifully described, has been extended to include a recognition of a noncommitant and interrelated psychological homeostasis and sociological homeostasis, contributing to the total personality. The thoughts, feelings, behavior and social relationships of patients, no less than their tissues and their body fluids, follow the same principle, the principle of continuous adaptative shifts and reciprocal balances.

When any one of these elements is disturbed from within or from without, the recovery of balance is attempted through a readjustment of all the others. The *agent provocateur* may be bacterium or a bayonet, a cancer cell or a seduction, a starvation of calcium or a starvation of love. Whatever the upsetting influence, many elements coöperate to restore the balance. Sometimes they overdo it, and the last state is worse than the first. For some aspects of this imbalance we have medical terms, for some aspects we have only sociological or common speech terms. But a meaningful diagnosis cannot be confined to the terms of any one discipline. To do so is to mislabel the condition, to misconceive its essential nature. What we conventionally call "disease" is sometimes the *agent provocateur*, sometimes the wound; it is sometimes the overaction of systemic defense measures and sometimes the consequences of mismanagement by relatives, friends and

even doctors. It is sometimes the picture of a triumphant malignancy, and sometimes that of a quiet renunciation, the sacrifice of a part for the whole, as with Polycrates' ring. All these we have called "the disease."

It is the imbalance, the organismic disequilibration, which is the real pathology, and when that imbalance reaches a degree or duration that threatens the comfort or survival of the individual (or his environment), it may be correctly denoted disease. The protean manifestations of that imbalance must be looked for by the doctor in all the spheres of human life, identified in their relationships, understood in their totality, recognized as symptoms of the imbalance, and labelled in any pragmatically useful way. But they must *never* be mistaken for *"the disease."*

THE ANIMAL KINGDOM, A RESERVOIR OF HUMAN DISEASE*

By K. F. MEYER, M.D., *San Francisco, California*

THE everlasting questions "why epidemics" and "in what manner has the human race become subject to multiform epidemization" encouraged for over a span of 40 years and on three continents the quest for answers. With the improvement of investigative methods, disease entities due to hitherto unknown infectious processes have been identified. To be sure, the number is steadily increasing, and there is no reason to believe that the total has as yet been reached. In the course of the search, it became clear that the parasitic diseases of man and animals are obviously a part of a broad evolutionary development. Again and again it has been discovered that animals in nature and those subsequently domesticated are a potent source of human illness and death. Ever since man's existence, he has been brought into intimate relation with the "living environment." Not only have animals furnished him the food and raw products of various sorts which enable him to work and to defend his existence, but they have approached him as injurious and destructive enemies. How different today are the answers when a mammal or an invertebrate is found to be a carrier or vector of a microbial or viral agent pathogenic for man.

Although Hippocrates and in particular Aristotle diligently compared the diseases of man and animals, the theurgical and cosmotelluric theories of pestilence predominated. Virgil described anthrax in sheep and indicated his knowledge of the spread from herd to herd. The folklore of the past contained many grains of truth, and Fracastoro's vivid account of the transmission of rabies: "When the outer skin is so torn by the bite of a dog that blood is drawn and contagion takes place through contact with the teeth and foam from the mouth of the rabid animal" succintly describes the relation of a disease of an animal to that of man. However, the highly religious attitude of the Middle Ages introduced a sharp distinction between the maladies of man and those of animals. While the Greek and Roman medical writers considered the similarity of disease processes in man and beasts, writers of the Middle Ages stressed the difference. Man, an image of God, could and should not be compared with the representatives of the animal kingdom!

Much later the discovery by Jenner that a disease of cows—cowpox—is related to a similar malady in man ushered in a new epoch. Aside from being a marvelous beginning because it furnished the basis for powerful protection against smallpox, it aroused, in the words of Jenner, great interest

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From The George William Hooper Foundation, University of California, San Francisco, California.

in "the prolific source of disease" that lingers in the animals of the forest "which may not originally have been intended for his associates." The new science began on top of a mountain, the benefits have been matched by subsequent achievements, but it is doubtful that the original crest will be surpassed. Leuckart's classical investigations in the middle of the nineteenth century demonstrated the significance of animal life cycles in human helminthic infections. The discovery of the presence of the parasite of filariasis in mosquitoes by Manson in 1879 and the first clear demonstration by Smith and Kilborne in 1893 that a protozoan disease of higher mammals is transmitted in a roundabout fashion by an intermediate host belonging to the group of the arthropods ushered in another epoch of phenomenal development. The application of the theory of the insect carrier led to the revelation of the secret of the tsetse fly disease, malaria, yellow fever, bubonic plague and typhus. A study of the ecology of the insect carriers or vectors involved far-reaching surveys of the animal kingdom. Totally unexpected situations came to light. Today the spread of the infections—rickettsial diseases, plague, encephalitides—from an ineradicable wild rodent or bird reservoir of infection is fully established. Fortunately, serious epidemics of these diseases can be suppressed by measures directed against the mosquitoes, the rats in cities and the lice on the human body.

The Infection Chain

The vast literature which deals with the newer knowledge of infection relationships is scattered throughout scientific journals and is not readily accessible to the clinician. To simplify orientation and to facilitate discussion, the essential facts have been summarized and tabulated under the heading "Heterogenous Infection Chains."

A brief explanation of this tabulation seems desirable.

Viewed by the naturalist, an infection is analogous to or identical with the *biological phenomena of parasitism* so widely existent throughout the animal and plant kingdoms. Until recently, the medically oriented microbiologist approached an infection from the standpoint not of the agent but of the altered state of the host—the disease. With the recognition of the so-called latent, inapparent or subclinical infections, and the infections without an infectious disease, this strictly utilitarian concept has been found untenable. The biologic definition of an infection as a host-parasite relationship offers a reasonable foundation on which to anchor the ever-growing store of knowledge. The transmission from host to host is incumbent upon all parasites; whether the transfer from the infected to the non-infected occurs directly or indirectly is immaterial. In principle, the relationship between the infection in the two hosts, one as "dispenser" and the other as "receiver," remains the same. One may conveniently designate the transmission from man to man or from animal to animal as a homogenous, and the transmission from an animal host to man or man to animal as a hetero-

genous infection chain. In table 1 the principal transmission chains are illustrated, and the known relationship of diseases of animals and man is elucidated by concrete examples. In the first paragraph the infectious diseases which may be conveyed from warm-blooded animals by the cutaneous, the alimentary or the mucosal aerogenic routes to man are listed. The name of the disease is followed by the species of animal which serves as the principal "dispenser" of the infective agent. This grouping is incomplete but it does comprise most of the known bacterial virus infections. In the last section the helminthic invasive diseases are considered. In order to avoid unnecessary confusion in the interpretation of an already complicated tabulation, the name of the bacterial or virus agent is usually omitted. Since this group embraces infections which are variable with respect to the disease incitant, mode of transmission, pathways of infection and epidemiology, it is possible to give but a few general characteristics which would equally describe all the representatives of the category.

The following facts are noteworthy:

(*a*) The diseases of highly organized mammals not only unfavorably affect the health of man, but through their serious economic effects also injure his welfare. Financial investment in animals is large; millions of

TABLE I

Heterogenous Infection Chains

Ia. *Highly organized: Homeothermic mammals*

animals	—	man	Passage usually broken

(1) Tuberculosis: Cattle
(2) Brucella infections (*a*) Bang's disease: Cattle, hogs, horses, dogs?
(*b*) Malta fever: Goats, sheep, hogs, dogs?
(3) Salmonella infections: Dogs, cats, cattle, hogs, sheep, rats, mice
(4) Swine erysipelas: Hogs, sheep?, [fish]
(5) Anthrax: Cattle, sheep, hogs, minks, others
(6) Plague: Wild rodents
(7) Pasteurelloses (*Pasteurella multocida*): Cats, dogs, rabbits
(8) Pseudotuberculosis: Cats, rodents?
(9) Tularemia: Cotton-tail rabbits, other mammals
(10) Glanders: Horses, mules
(11) Melioidosis: Rats, cats, dogs, horses
(12) Listerelloses: Cattle, rodents
(13) Trichophytosis: Horses and cattle in rural areas, cats and dogs in urban areas
(14) Rabies: Dogs, other carnivores, vampire bats, others
(15) Foot and mouth disease: Cattle, hogs
(16) Lymphocytic choriomeningitis: Gray mice, dogs?
(17) Pernicious anemia: Horses
(18) Virus B: Monkeys (*Macacus rhesus*)
(19) Sore mouth: Sheep
(20) Pox diseases—vaccinia: Cattle
(21) Leptospirosis: Rats, mice, dogs, cats, pigs, foals, horses, foxes, cattle
(22) Rat bite fever (*Spirillum minus*, *Streptobacillus moniliformis*)—Sodoku: Rats, mice
(23) Balantidiasis: Monkeys, domestic pigs
(24) Espundia (*Leishmania americana*): Dog, agouti (Daryprocta)
(25) Q fever group (*Coxiella burnetii*): Cattle [aerogenic transfer? ticks?]
(26) Toxoplasmosis (Toxoplasm): Mammals [arthropods?]

TABLE I—*Continued*

Ib. *Highly organized: Homeothermic birds*

bird — man and bird — man — man

and bird — mammal — man

(1) Tuberculosis: Birds, barnyard fowls
(2) Psittacosis: Parakeets, South American and Australian psittacine birds, canaries, finches, fulmars, pigeons, chickens, ducks
(3) Fowl pest—Newcastle disease: Barnyard fowls
(4) Favus: Chickens
(5) Salmonella infections: Ducks, turkeys, chickens, pigeons
(6) Tularemia: Gamebirds
(7) Toxoplasmosis: Birds

II. *Lowly organized: Arthropod vectors*

A. Mechanical transfer

Subgroup 1

animal — insect — man

Anthrax
Vector: Biting flies (Stomoxys, Tabanus)
Tularemia
Vector: Deer fly (*Chrysops discalis*)

insect — insect — man

Dermatobiasis (*Dermatobia hominisis*)
Vector: Psorophora—mosquitoes

man — flies — man

Dysentery, cholera, typhoid, poliomyelitis
Vectors: *Musca domestica, Chrysomyia megacephala, Aphiochaeta ferruginea, Phormia regina?, Phoenicia sericata*

man — insect — man

Yaws (*Treponema pertenue*)
Vectors: Hippelates sp., Musca sp.
Follicular conjunctivitis (virus)
Vector: Hippelates sp.

B. Cyclopropagative multiplication in vector

Subgroup 2

host — insect — man

Malaria (*Plasmodium vivax, P. malariae, P. falciparum, P. ovale*)
Vectors: *Anopheles freeborni, A. quadrimaculatus, A. punctipennis* in United States, *A. gambiae* in Africa, *A. pseudopunctipennis* in South and Central America, *A. punctulatus* in Polynesia, *A. subpictus* and *A. maculatus* in Java and Malaya
Trypanosomiasis (*Trypanosoma gambiense, T. rhodesiense*)—African sleeping sickness
Vectors: *Glossina tachinoides, G. morsitans* in Africa
Chagas disease (*Trypanosoma cruzii*)
Vectors: Reduviidae—*Mestor megistus, Triatoma infestans* in South America
Hosts: Dogs, cats, armadillos, pack rats
Leishmaniasis (*Leishmania donovanii, L. infantum, L. tropica*)—Kala-azar, oriental sore, visceral and cutaneous leishmaniasis
Vectors: Phlebotomus (*P. major, P. perniciosus*)
Contamination—infection
Hosts: Dogs, gerbilles, ground squirrels

TABLE I—*Continued*

C. Propagative multiplication in vector

man — insect — man

Yellow fever (virus, "amaril")—urban type
Vector: *Aedes aegypti*
Dengue (virus)
Vectors: *Aedes aegypti, A. albopictus, A. scutellaris?*
Sandfly fever (virus)
Vector: *Phlebotomus papatasii*
Relapsing fever (*Borrelia recurrentis*)
Vector: *Pediculus humanus*
Epidemic typhus (*Rickettsia prowazekii*)—classical typhus, old world typhus
Vectors: *Pediculus humanus*, var. *corporis* and var. *capitis* by fecal droplets

Subgroup 3

vertebrate host — insect — man

Yellow fever (virus)—rural type, jungle type
Primate-mosquito cycle
Hosts: Red howler (*Mycetes seniculus*), marmosets (*Callithrix aurita*) in South America, red-tail monkey (*Cercopithecus nictitans impangae*) in Africa, other primates
Vectors: *Aedes leucocaelenus, Haemagogus capricorni* and *H. spegazzini* in South America, *Aedes simpsoni, A. africanus* in Central Africa
Western equine encephalomyelitis (virus)
Principal hosts: Chickens, other birds
Vectors: *Culex tarsalis, Aedes dorsalis, Culiseta inornata, Triatoma sanguisuga, Dermanyssus gallinae?, Liponyssus sylviarum?, L. bursa?*
Accidental hosts: Horses, mules, deer, hogs, prairie chickens, man
Eastern equine encephalomyelitis (virus)
Reservoir: Birds?
Vector: Aedes?
Accidental hosts: Horses, mules, pigeons, pheasants, man
St. Louis encephalitis (virus)
Principal hosts: Chickens, other birds
Vectors: *Culex tarsalis, C. pipiens, Aedes dorsalis, Culiseta?, Dermanyssus gallinae?, Liponyssus sylviarum?*
Japanese B. encephalitis (virus)
Reservoir: ?
Vectors: *Culex pipiens, C. tritaeniorhynchus, Aedes togoi?*
Susceptible host: Horses
Enzootic hepatitis (virus)—Rift Valley hepatitis
Reservoir: Sheep, cattle
Vector: *Mansonia fuscopennatus*
Other virus infections (California, West Nile, Semiliki Forest, Columbian encephalitis viruses)
Possibly similar chains as others in this subgroup
Vector: Mosquitoes
Carrion's disease (*Bartonella bacilliformis*)
Reservoir: ?
Vector: *Phlebotomus verrucarum*

Subgroup 4

flea — rodent — man

and rodent — insect — man — man

and rodent — man — man

Plague (*Pasteurella pestis*)
Vectors: *Xenopsylla cheopis, Nosopsyllus fasciatus* on rats, *Diamanus montanus*, Thrassis sp., Oropsylla sp. and other sp. on wild rats, lice, ticks
Hosts: Rats (*Rattus norvegicus, R. alexandrinus*), ground squirrels (Citellus sp.), marmots and prairie dogs (Cynomys sp.), chipmunks (Eutamias sp.), tree squirrels (Sciurus), native rats and mice (Neotoma sp., Microtus sp.)

Subgroup 5

TABLE I—*Continued*

Subgroup 6

rat — flea — man — louse — man

and rat — mite — man — [ ] — rat

Murine typhus (*Rickettsia typhi*)—endemic typhus, Tabardillo in Mexico, Maxy's disease in United States, Manchurian typhus
Vectors: *Xenopsylla cheopis, Pediculus humanus* (*Liponyssus bacoti*), *Polyplax spinulosus*
Coproctic transmission

D. Propagative multiplication and ovarian transfer in vector

Subgroup 7

host — tick — tick — man

Laboratory: mouse — man

Louping ill (virus)
Vector: *Ixodes ricinus*
Russian spring-summer encephalitis
Vectors—reservoir?: *Ixodes persulcatus, Dermacentor silvarum, Haemaphysalis concinna*
Hosts: Rodents, birds

Subgroup 8

tick — tick — rodent — tick — man

and rodent — man

Relapsing fever in United States (*Borrelia turicatae, B. hermsi, B. parkeri*)
Vectors: *Ornithodorus turicata* in Texas and Kansas, *O. hermsi* in California, *O. parkeri* in Wyoming, Montana and California, *O. talaje* in Arizona
Hosts: Chipmunks, golden mantle squirrels, ground squirrels
Relapsing fever in Africa, Spain and Central America (*Borrelia duttoni, B. kochii, B. berbera, B. persica, B. hispanica, B. venezuelensis*)
Vectors: *Ornithodorus erraticus, O. moubata, O. pallipes, O. marocanus, O. venezuelensis*

Subgroup 9

tick — tick — rodent

and tick — rodent — fly — man and tick — man

and rodent — man and rodent — water — man

Tularemia (*Bacterium tularense*)
Vectors: *Dermacentor andersoni, Chrysops discalis*
Hosts: Cotton-tail rabbits, hares, squirrels, coyotes, rats, other mammals, birds

TABLE I—*Continued*

Subgroup 10

tick — tick — rodent — tick — man

(*a*) *Tick typhus* (*Rickettsia rickettsii*)—Rocky Mountain spotted fever
Vectors: Western spotted fever, *Dermacentor andersoni*
Eastern spotted fever, *Dermacentor variabilis*
Hosts: Rabbits, ground squirrels, other rodents, dogs
Fièvre boutonneuse (*Rickettsia conorii*)—Marseilles fever
Vector: *Rhipicephalus sanguineus*
Host: Dogs
South African tick bite fever (Rickettsia sp.)
Vectors: *Amblyomma hebraeum, Boophilus decoloratus*
Kenya fever (Rickettsia?)
Vector: *Rhipicephalus sanguineus*
Host: Unknown
Sao Paulo typhus—Brazilian spotted fever
Vectors: *Amblyomma cajennense, A. striatum*
Hosts: Opossums, rabbits, cavies, plain dogs
North Queensland tick typhus (Rickettsia?)
Siberian tick typhus?
Indian tick typhus?

Subgroup 11

rodent — mite — mite — man

(*b*) *Tsutsugamushi disease* (*Rickettsia tsutsugamushi*)—mite typhus, rural typhus, scrub typhus, mite fever of Japan, Malaya, Burma, Sumatra, New Guinea and adjacent islands
Hosts: Microtus, Rattus sp., Hadromys, Bandicota, Tupaia
Vectors: *Trombicula akamushi, T. deliensis*

Subgroup 12

mouse — mite — man Probably transovarian in vector, not yet demonstrated

(*c*) *Rickettsial pox* in New York City (*Rickettsia akarii*)
Vector: *Allodermanyssus sanguineus*
Host: *Mus musculus*

E. Helminthic infections: Homeothermic and poikilothermic animals

Subgroup 13

animal — man — animal and animal — man

Tapeworms (*Taenia saginata, T. solium*)
Hydatid worms (*Echinococcus granulosus*)
Trichinosis (*Trichinella spiralis*): Hogs, bears, dogs
Dog hookworm (*Ancylostoma braziliense, A. canium*)

Subgroup 14

man — arthropod — man

and animal — arthropod — man

Developmental in vector, no multiplication
Filariasis (Wuchereria): Culex sp., *Aedes scutellaris*, Taeniorhynchus sp.
Onchocerciasis (*Onchocerca volvulus*): *Simulium damnosum*
Loa worm (Loa loa): *Chrysops dimidiata*
Guinea worm (*Dracunculus medinensis*): Cyclops
Dog tapeworm (*Dipylidium caninum*): *Ctenocephalides canis*
Rat tapeworm (*Hymenolepis diminuta*): *Xenopsylla cheopis*

Subgroup 15

man — snail — man

Schistosomiasis (*Schistosoma japonicum, S. haematobium, S. mansoni*)

TABLE I—*Continued*

Subgroup 16	man — snail — fish — man	*Chinese liver fluke* (*Clonorchis sinensis*)
Subgroup 17	man — snail — arthropod (crab) — man	*Lung fluke* (*Paragonimus westermani*)
Subgroup 18	man — snail (vegetation) man	*Large intestinal fluke* (*Fasciolopsis buskii*)
Subgroup 19	sheep — snail (vegetation) man	*Sheep liver fluke* (*Fasciolopsis hepatica*)
Subgroup 20	man or dog or cat — copepod — frog or fish	(Sparganum) man *Broad fish tapeworm* (*Diphyllobothrium latum*) *Mason's tapeworm* (*Diphyllobothrium mansoni*)

citizens depend upon the breeding and raising of farm animals as their means of livelihood. These citizens are profoundly affected by the toll of animals taken by disease. Human health is greatly influenced by such foods as meat, milk, butter and cheese. These foods are relatively expensive since a considerable part of the cost is related to disease losses. It has been estimated that the annual cost of these losses exceeds one billion dollars. Huddleson (1947) estimated that brucellosis in one year deprived the milk-consuming public of 222,804,000 pounds of market milk. Equally significant are the data on the losses of calves. In Michigan alone in only a year, 108,000 infected cows of breeding age lost 16,240 calves; hence, 1,299,200 pounds of veal failed to reach the consumer. Further proof that brucellosis is a great destroyer of potentially available meat is furnished by the staggering fact that on hog-raising farms 82 per cent of the expected pig crops may be lost. Whatever the losses may be in other groups, it is clear that disease entails a heavy economic burden upon agricultural industry and directly on the economy of the country. Some progress has been made through education of the farmer concerning the economic losses, but he remains unaware of the health hazards of having infected livestock on his premises. Data recently collected in Iowa and Indiana reflect the high incidence of infections associated with diseases of domesticated animals in this occupational group. In nearly every communicable disease, public health efforts have lowered morbidity and mortality. The only diseases in which a noteworthy record has not been achieved are those of animal origin. Every physician has a share in the economic and educational problems created by the diseases of domesticated animals.

(*b*) The majority of microörganisms or viruses responsible for the diseases are capable of infecting in nature a great many animal species and, under experimental conditions, a variety of zoölogically unrelated hosts. Man only accidentally and rarely becomes part of an infection chain.

(*c*) With the exception of the poxes, foot-and-mouth disease and glanders, the infections of the mammals frequently are chronic, and exhibit an outstanding tendency to remain latent or subclinical. The apparently healthy, though infected animal—a carrier or shedder—bears an epidemiologic relationship with the single or group infections of man. Early acute, but mild and atypical stages of the animal disease may be equally dangerous.

(*d*) After the heterogenous infection chain is formed, it seldom continues as a homogenous one or becomes again heterogenous. Human-to-human infections are rare. Outside the usual host cycle, the restricted mode of transmission is in part responsible for this break. Infections with bovine tubercle bacilli were formerly considered closed processes, conveyed only from animal to man, but in view of observations by Griffith and Munroe (1944) and others, man-to-man infection is now admitted. Rabies virus has occasionally been demonstrated in the saliva of children (Duffy et al., 1947) but authentic human-to-human transmissions have not been reported. To be sure, there is reason to suspect that the direction of the usual heterogenous infection chain may be reversed—infection of tuberculosis-free cattle by dairy hands with open bovine pulmonary tuberculosis. With this exception and possibly others as yet unrecognized, the disease agents which may operate in heterogenous chains maintain the species through continuous passages through the animal host. When the course is diverted and man becomes the host, it is likely to end blindly. As far as has been ascertained, with the exception of bovine tuberculosis, infection does not result from the exposure of a susceptible animal to a diseased human being.

(*e*) The clinical and anatomical character of the disease in man is quite similar to that in the animals. A change in host apparently fails to alter the principal diagnostic signs, provided the portal of entry of the parasites is the same. Some authors have pointed out that the brucella infections present noteworthy exceptions. In man, they say, it manifests itself as a septic fever, while in cattle as a localized process in the udder or in the placenta. These differences may be only relative. Very little is known concerning the early clinical course of *Brucella abortus* infection in cattle. According to Thomsen, cattle and, according to van der Hoeden (1946), horses infected with the brucella organisms may have fever of the undulating type. Blood cultures are frequently positive. Comparative clinical studies of the diseases listed in the first group show that no significant changes take place in the disease when the parasite changes hosts.

(*f*) At least 75 diseases of domestic and wild animals are of potential public health significance. The control by eradication appears to be easy in some, is more difficult in others and when wild rodents, monkeys and

birds act as reservoirs it is impossible. By destroying the infected animal, for example, the highly contagious foot-and-mouth disease has repeatedly been stamped out in the United States. Much faster progress has been made in the elimination of tuberculosis from cattle than has been possible with the same disease in man, by slaughtering the infected animal. Diminution of dense rodent and flea populations close to human settlements with newer rodenticides and insecticides may eliminate endemic typhus and plague. Whenever the principle of destroying the animal host is impractical and too costly, in some diseases regular immunization of exposed livestock may prove effective. Large-scale vaccination has reduced the number of outbreaks of anthrax in rural areas and with it the problem of human infections. It is earnestly hoped that the same may follow the use of calfhood vaccination against brucellosis. However, in the face of vast reservoirs of disease such as yellow fever in the wild regions of Africa and South America, or of sylvatic plague on nearly every continent, the hope of wiping them out becomes untenable. Measures directed against the arthropod vector and the use of protective vaccines for the exposed human population give, in the light of wartime experiences, some assurance that serious epidemics may be averted.

Diagnosis and Treatment of Diseases of Animals Transmissible to Man

It would, no doubt, be profitable and most gratifying to review the entire group of the diseases listed, but since the time is limited a selection has been made of a few infections which have attracted attention in recent years. Since the majority of practicing physicians rarely encounter these infections, the problem of diagnosis deserves special consideration. Although the diagnosis follows the pattern set for all infectious diseases, certain points deserve emphasis. A good epidemiological history may be most useful. This presupposes more than perfunctory knowledge of the mode of transmission. Experience has taught that the "prepared mind" is essential in spotting the accidental transmissions from animal to man. If a patient contracts a respiratory infection characterized by cough, fever, muscle aches and headaches, the following diagnostic possibilities should be considered: influenza, atypical pneumonia and psittacosis. In influenza the only disease source is another human being, and the incubation time is short. In contrast, atypical pneumonia has a longer incubation time—10 days to 3 weeks. Patients' association with birds, not merely psittacine varieties, suggests that the infection is psittacosis. Unfortunately, neither history nor physical examination makes it possible to recognize the nature of the infective agent. However, laboratory tests, which identify the specific etiologic factors, or serologic examinations, which indirectly indicate the nature of the infection, are available for diagnosis of the most important animal diseases transmissible to man. Promptness in diagnosis assures early efficient treatment.

Fortunately, with the advent of sulfonamide drugs and antibiotics, treatment of many of these infections has been effectively and dramatically improved. It will be the aim of the presentation which follows to emphasize some diagnostic and therapeutic aspects of the selected diseases.

Salmonella Infections: Human infection with salmonella is widespread, and the majority of outbreaks of food poisoning and endemic enteritis due to this group of organisms follow the consumption of food directly or indirectly associated with infection of some animal. In the United States poultry and other birds cause many cases. Barnes said that he considered the domestic fowl "the main animal reservoir of organisms affecting man." American spray-dried eggs during the war caused outbreaks of food poisoning in various places. On the other hand, the brilliant epidemiological studies by Watt in the Rio Grande Valley incriminate with equal force dogs, cats and ducks. Over 2 per cent of each of these animals were proved to harbor many varieties of salmonella in that locality. Some investigators found turkeys to harbor 23 types of salmonella (Pomeroy and Fenstermacher); turkey eggs from 8 per cent of the birds examined harbored the *Salmonella pullorum*. Market pork examined in Lexington, Kentucky, yielded salmonella (8 varieties) in 10 of 170 samples. One of 40 samples of beef was infected with *Salmonella seftenberg* (Cherry et al.). In spite of this widespread incidence of infection in domestic animals and their products used for food, the apparent infrequency of salmonella food poisoning requires some explanation. Human volunteer experiments by Hormaeche, Peluffo and Aleppo demonstrated that adults might ingest as many as 4,000,000,000 organisms without suffering from any symptoms at all, or from any other than mild afebrile diarrhea. Infants and old persons, however, appear to be considerably more susceptible than those in the middle group, and fatalities are restricted to these two age groups. In typhoid, cholera and dysentery, minute amounts of infective material may suffice to cause disease, but in food poisoning, large doses are generally necessary (Savage). The bacteriological diagnosis by means of modern selective culture media, as a rule, offers no difficulties, provided examinations of stool specimens obtained with rectal swabs are made repeatedly. Identification of the salmonella type has shown that *Salmonella typhi murium* is more often responsible for food poisoning than any other type. There is no specific treatment and the eradication of the animal reservoirs may offer insurmountable difficulties. Thorough systems of food inspection, refrigeration, pasteurization or cooking, which may succeed in reducing the number of the organisms, may be used as precautionary measures.

Anthrax: Anthrax, once an industrial hygienic problem because infected animal products were taken into tanneries, wool mills, glue factories, feed supply stores (infected bone meal) and such places, is now a problem of rural areas. The statistics of Smyth show a steady increase in the occurrence of agricultural anthrax during the 20 year period from 1919 to 1938,

but a definite decrease occurred during the five year period from 1939 to 1943. Wider application of preventive vaccination and other control measures during recent years is responsible for the improvement. The death rate for agricultural anthrax is higher than that for industrial anthrax and, unfortunately, continues to be high because diagnosis and treatment are delayed. Necessity for prompt recognition of human infections and efficient therapy with penicillin, which is more readily available than anthrax serum, places the problem of anthrax in the hands of the medical practitioner.

Plague: As a cause of death, plague plays a very subordinate rôle in the United States; during the past 15 years only 20 human cases have been definitely recognized, despite the fully established fact that plague is enzoötic in the wild rodent population over at least 14 Western states of the Union and in one province in Canada. Presence of this form of plague, now described as sylvatic plague, was suspected in 1903 and then definitely proved in 1908 in California. The official records for the period 1900 to 1947 attribute 48 cases of bubonic and 13 of pneumonic plague to the distribution of the rodent disease. Since 1935 human plague, most likely due to some contact with wild rodents, has been seen in Idaho (1 case), Nevada (1 case), Oregon (1 case) and Utah (2 cases). The question is constantly raised: What are the potential dangers of the sylvatic plague reservoirs? No definite answer has as yet been given. Disconcerting is the fact that during the past 15 years the few cases of human plague which have been recognized and reported have frequently served as sentinels to announce the dynamic activity of the primary rodent disease in areas where it had not previously been known to exist. The death of a sheep herder led to the demonstration of marmot plague in Oregon. A case of bubonic plague in southwest Utah, one in Idaho and others in San Bernardino, Placer and Siskiyou Counties in California, as well as in Douglas County, Nevada, were connected with previously unrecognized sylvatic plague pockets. Epizoötics of wild rodent plague in which the fields and canyons are littered with carcasses of dead squirrels and the entrances to their burrows swarm with infected fleas rarely produce human infections. Why the disease fails to develop in man under such circumstances remains an unsolved mystery. Some unknown inherent weakness in the linkage formed by the flea must be responsible for the extreme infrequency of human infection in the open country. Domestic premises in rural communities, and cottages and cabins in summer resorts are the places where the infection most frequently has been contracted. The participation of mice and their ectoparasites in the exchange of the plague bacillus must be constantly kept in mind. A fatal bubonic plague infection in a boy residing in Siskiyou County was, in all probability, contracted in a barn where field mice exchanged their ectoparasites with those traceable to infected squirrels living in the adjacent fields and forest. On the other hand, direct contact in skinning or handling squirrels, bite wounds sustained through handling rodents or predators and

picking magpie nests have been associated with infections. The sporadicity of the outbreaks of bubonic plague in sections of the country, where it has never been identified and is seldom seen, makes it understandable why the diagnosis of human plague is so frequently missed during its course, and is made only after recovery or death. In my experience during the past 10 years in at least 14 of the 20 cases reported, mistaken diagnoses had been made before plague was recognized. At least in the West, every physician practicing in rural areas where squirrels are likely to be decimated by epizoötics should constantly keep in mind that a painful edematous axillary or inguinal enlargement of the lymph node may be caused by plague. He should likewise remember that surgical treatment interferes with the local defense mechanism and is only too often followed by septicemia. Finally, early diagnosis is of greatest importance, not only to the patient whose recovery may depend on the early administration of streptomycin or sulfadiazine, but also to his family, physician and community. In case plague-pneumonia, secondary to the bubonic form, goes unrecognized an enormous number of highly virulent plague bacilli may be disseminated through the sputum and within a few days the infection chain may involve scores of victims. The outbreaks of pneumonic plague in Oakland and Los Angeles are excellent examples of what will happen when bubonic plague is surgically treated, or when primary plague pneumonia is diagnosed as double lobar pneumonia. By puncturing the bubo in its earliest stage with an 18 gauge needle, a small amount of edematous fluid may be aspirated readily and used for microscopic examination. The plague bacillus derived from these lesions has a characteristic morphologic appearance: round, ovoid or short safety-pin-shaped rods, marked bipolar staining. With streptomycin now available as an outstanding specific therapeutic agent, the high case fatality rate of from 50 to 100 per cent for bubonic, carbuncular and pneumonic plague may be reduced to less than 5 per cent. Without delay, treatment consisting of intramuscular injection of 0.5 gm. every 6 hours for five to eight days or oral administration of sulfadiazine in doses adequate to create concentrations in the blood of from 10 to 15 mg. per 100 c.c. should be instituted.

Whatever disagreement may exist regarding the magnitude of the menace of sylvatic plague, it is imperative to protect rural communities against exposure. The maintenance of so-called rodent-free belts around towns is imperative. Control of dense rodent and flea populations close to human settlements with the newer rodenticides and DDT demands constant follow-up in order to be effective. Ecologic study of sylvatic plague may lead to the discovery of the type of hindrance which will in time liberate rural communities from a hazard which unfortunately is unrecognizable and immeasurable.

Pasteurelloses: Human infections with *Pasteurella multocida* are being more frequently recognized (Levy-Bruhl; Weber; Schipper). In 55 cases (five deaths), not always proved according to modern methods of bacteri-

ology to be cases of pasteurellosis, the infection was *local* with and without generalized symptoms. In almost half, animal bites were precursors of infection: it was proved that at least 21 of the infected persons were bitten by cats, four by dogs, one by a rabbit and one by a panther. Exposure to infected bovine animals, pigs or rabbit carcasses (muscle particularly) or consumption of infected rabbits brought on enteritis, conjunctivitis, appendicular abscesses and other manifestations. The generalized infections, symptoms of which vary widely from protracted, recurrent chills and fever to pneumonia and empyema (12 cases), meningitis (7) and puerperal sepsis, have been reported mainly from Europe. The sources of infection remained undetermined. Generalized infections frequently have proved fatal. Meningitis associated with pasteurella, of which seven cases have been recorded, is usually sequel to skull fracture or sinusitis. It is not unlikely that the offending organism which induces meningitis subsequent to skull fracture comes from the nasal passages. Topley and Wilson observed the persistent carrying of a pasteurella in the nose of an animal caretaker. Particularly interesting is the fact that *Pasteurella multocida* apparently may lie dormant in the tissues for months and only after trauma of subacutely infected tissues give rise to acute infection. Localized human pasteurella infections, which may produce only phlegmon and abscess, are only too frequently complicated by osteomyelitis (Hansmann and Tully). It was epidemiologically proved that at one time in the City of Munich, where many cat bite wounds had been noted (Weber), 75 per cent of the cats harbored pasteurella organisms in their nasal passages. Pasteurella obtained from the throats of animals have proved sensitive to 0.2 unit of penicillin per milliliter or less (Schipper).

Pseudotuberculosis: Dujardin-Beaumetz, Ballet and Cébron (1938) listed eight infections in man, all beyond question pseudotuberculosis, with the following geographic distribution: one in Japan, three in Hamburg, Germany, two in Czechoslovakia and two in Austria. All terminated fatally. These authors also mentioned the case reported by Albrecht in which the resected appendix of a 15 year old child, who had intimate contact with a cat, was proved by guinea pig inoculations to contain *Pasteurella pseudotuberculosis.* They also reported a case of fatal infection observed in France. To this list of 10 must be added three cases reported and one unreported in the United States (Topping et al.; Moss and Battle; Snyder and Vogel; Mason and Meyer) and one of mixed plague-pseudotuberculosis infection recorded by Macchiavello in Brazil. The descriptions of the 14 cases indicate that vague prodromal malaise was followed by abrupt febrile onset with headache, chills, general pains and occasional catarrhal symptoms. The fever was irregular or "septic," the temperature at times reaching 105° F. Anorexia, abdominal tenderness, constipation and variable degrees of leukocytosis usually were noted. Within a few days after onset the liver, and sometimes the spleen as well, became palpable and tender. Death was usually preceded by icterus, toxemia and stupor. In 11 cases the infection terminated fatally

between 10 and 18 days after symptoms were evidenced; in one, early in the third month. Diagnosis was established early by means of blood cultures and later by serum agglutination tests. Still other manifestations were septicemia, effusions into serous cavities, bronchitis, pulmonary engorgement and edema and parenchymatous changes in the liver, kidneys and myocardium. At autopsy pathognomonic caseous necrotic foci, 1 to 10 mm. in diameter, were scattered throughout the enlarged liver, spleen, mesenteric lymph nodes and occasionally in the pancreas. Hemochromatosis was frequently noted. In some cases ulcers had formed in the small intestines and colon. With the exception in the cases described by Macchiavello, all infections were abdominal, a fact which supports the contention that they were acquired via the digestive tract. In two cases the patients were known to have had contact with cats or garden soil contaminated with their excreta, while another patient had eaten rabbits.

According to recent tests, streptomycin (6 to 12 micrograms per cubic centimeter) inhibits rodent strains of pseudotuberculosis and hence should be useful in the treatment of these infections.

Rabies: That rabies as a prevalent animal disease is a problem in some communities is evidenced by the continuing demand for information and advice concerning postinfectional treatment with vaccine, as well as planning of effective rabies control programs. The knowledge that rabies is invariably fatal once it has developed makes it one of the most feared and notorious of diseases. The physician is usually confronted by the problem of estimating the possibility of infection in the bite victim; he must at the same time decide on the necessity for prophylactic treatment: two difficult decisions. Rhodes (1946) in a critical analysis of the value of human antirabies treatment emphasized a number of significant facts, among them that the mortality from rabies in untreated persons bitten by rabid animals is on the average no more than 15 per cent, and may well be less. Doubtless, in the past a considerable number of persons must have been treated with vaccines of very low immunizing potency. Furthermore, persons have doubtless been treated with antirabies vaccines who were not at risk from rabies. Though he concluded that many variable factors make any accurate appraisal of antirabies treatment in man impossible, he did suggest that on the evidence at present available, it is justifiable to continue to regard antirabies treatment as being of some value in the prevention of rabies, although it may not necessarily act by the orthodox process of active immunization. There is no justification for withholding treatment from persons thought to be at risk. The treatment as at present employed could probably be considerably improved, partly by the more frequent use of immune serum, and partly by the increased use of more potent vaccines. The vaccines found to be most effective in animal experiments are not yet generally used in human treatment. It is well known that in rare instances administration of rabies vaccine has resulted in neuroparalytic accidents. In recent years, postpas-

teurian myelitis has been encountered more frequently. Consequently, a justified reluctance to administer postinfectional vaccination as an appeasement of one's conscience has developed. A concerted effort should, therefore, be made to control and possibly eradicate rabies. On a nationwide basis, the three major steps, (1) control of stray dogs, (2) vaccination of all dogs and (3) reduction of wild animal population when it is the reservoir, must be taken. The control of rabies is largely dependent on public interest and coöperation. An organized program of vaccination requires the fullest support of the medical profession and in particular the family physician whose advice to the owner of a dog is invaluable. Vaccination of dogs has proved its worth during the past few years. A single injection will protect 90 per cent of the dogs for one year, while three injections offer almost 100 per cent protection. On a voluntary basis, a program of canine vaccination in Massachusetts has freed that area from the disease for the first time since its introduction there in the eighteenth century. Alabama's experience with the vaccination program was similarly gratifying.

Rickettsial Diseases: The rickettsial diseases constitute an important and extremely interesting group of infections conveyed by arthropod vectors. There are five main categories listed under subgroups 3, 6, 10, 11 and 12. The first group, predominantly louse-borne, includes classical European endemic and epidemic typhus, the widespread flea-borne murine typhus of the Southern, Southeastern and Western United States (Beck and Van Allen). Mexican tabardillo and similar diseases in every part of the world belong in the second group. The third or spotted fever group contains the tick-borne diseases—both western and eastern Rocky Mountain spotted fever, Sao Paulo typhus, fièvre boutonneuse of the Mediterranean, South African and Kenya tick fever and others. The fourth group, borne by mites, includes scrub typhus, rural typhus of Malaya and rickettsial pox recently observed in the heart of New York. The fifth group—the Australian Q disease, nine-mile fever of Montana and Q fever of the Mediterranean, Greece, and the quite recently recognized infections on the American continent—probably constitutes a special category.

Rickettsiae are visible by ordinary microscopic examination and resemble bacteria in shape, but they are much smaller than influenza bacilli. Their growth requirements are only fulfilled by an obligate intracellular habitat. It has not been possible to grow them in the absence of living or at least surviving cells as, for example, the yolk sac of the embryonated chicken egg. In the invertebrate host they invade the cells of the intestinal tube and multiply within. Some arthropod hosts suffer by their presence; others do not. When transferred to man from the arthropod hosts, they cause disease with characteristic lesions. Since rickettsiae parasitize primarily the cells of the blood vessels, they give rise to vasculitis in the arterioles which leads to thrombosis and eventually necrosis. Perivascular infiltration by mononuclears, plasma cells and polymorphonuclear elements produces tubercular

nodules in the organs and tissues. These changes take place in the skin and cause the characteristic rash in the mucous and serous membranes and hemorrhages in various organs and in the central nervous system. The participation of the neuroglia cells in the reaction gives rise to the mental symptoms. The illness resulting is clinically characterized by an incubation period of one to three weeks, by sudden onset of headache and muscular pains and by fever lasting up to three weeks and usually ending by rapid lysis or crisis. In severe cases, a characteristic rash appears on about the fifth day after the other symptoms are manifest. Sera agglutinate certain strains of proteus (Weil-Felix reaction) and give complement-fixation reactions with specific antigens prepared from the respective strains of rickettsiae. The location of the maculopapular rash, first on the wrist or ankles, suggests tick-borne spotted fever, while a roseola rash on the trunk is diagnostically indicative of typhus. The clinical pathology of the rickettsial disease is very interesting; in all severe cases hypoproteinemia, drop in the concentration of plasma chlorides and increase in that of nonprotein nitrogen accompany the dehydration. Correction of these disturbances should be attempted by means of an adequate fluid intake and blood plasma transfusions. Many efforts have been made to find a substance of therapeutic value in rickettsial disease. After early trials with para-aminobenzoic acid made by the United States of America Typhus Commission Unit in Cairo, Egypt, the conclusion was reached that large doses exert a definite beneficial effect in the course of louse-borne typhus if treatment is started in the first week of illness. The drug, which has also been used at other centers, has been given by mouth; initial doses varied from 4 to 8 gm. and subsequent doses of 2 gm. were administered every two hours. Concentrations of from 10 to 20 mg. per 100 c.c. were maintained until the illness subsided (Snyder et al.). Since its effectiveness was demonstrated in louse-borne typhus, PABA in form of the sodium salt or in other conveniently administered forms has been successfully used in the treatment of endemic typhus (Smith and others), Rocky Mountain spotted fever (Greeley) and scrub typhus (Tierney). Curative action of the pure chemical due to its low toxicity has been excellent, provided therapy is begun early and blood concentrations of from 10 to 20 mg. for typhus and 35 to 40 mg. per 100 c.c. for Rocky Mountain spotted fever are maintained throughout the entire course of therapy. Leukocyte counts should be made daily; if the cell count falls below 3,000 serious consideration should be given to termination of therapy. The urine must be kept slightly alkaline to prevent the formation of crystals in the renal tubules. Preliminary experiments on embryonated eggs and on mice infected with the rickettsial agents of scrub typhus, epidemic and endemic typhus, Rocky Mountain spotted fever and rickettsial pox revealed that the new antibiotic, chloromycetin, has a remarkable therapeutic effect on these infections. Its low toxicity, its absorption from the alimentary tract and its beneficial effect even late in the disease suggest that it may be valuable in the treatment of patients (Smadel and Jackson).

The preventive measures against these infections are directed chiefly toward (1) elimination of the reservoirs—insect and mammalian and (2) specific immunization. The extraordinary effectiveness of the chemical DDT in destroying lice on garments and bedding has made obsolete the elaborate measures of delousing used in the past. Elimination of rats and rat fleas through spraying of rat holes or burrows and rat runs with DDT reduces the incidence of endemic typhus. Utilization of specific chemically-killed yolk sac vaccines has greatly reduced the incidence, severity and mortality of many of the most important rickettsial diseases except scrub typhus.

Q Fever: Q fever, originally discovered and described as a rickettsial disease in Queensland, Australia, in 1935, has risen in status from an infection of localized interest to one of world-wide importance. While ticks infected with *Coxiella* (*Rickettsia*) *burneti* were found in many parts of the United States before 1946, only a few naturally occurring infections have been established here. During the war the infection was assuming considerable importance when it was discovered to exist endemically and epidemically in the Mediterranean area and sporadically in Panama. Since then it has been proved to exist in Switzerland and Germany. Two explosive outbreaks of Q fever, one with 55 cases in Amarillo, Texas, in March, 1946 (Topping et al.), and a second in the stockyards of Chicago (Shepard), all infections more or less closely associated with the handling of cattle, focused attention on the probable prevalence of the infection in the United States. The failure to detect more cases in the past may possibly have been due to the use of a weakly reactive strain of the *Coxiella burneti* as antigen in the serological tests. The epidemiologic studies in 1946 produced no evidence of transmission by ticks, and it was thought that infection may have been incurred by inhalation of dust containing material contaminated by the excreta of infected cattle. Furthermore, the clinical observations disclosed that the disease picture was extremely varied, ranging from subclinical attacks and mild influenza-like illness with little evidence of pulmonary involvement through severe atypical pneumonia and pneumonitis to fatality (two in Amarillo). Convalescent sera of patients gave complement-fixation reactions, which reached the maximal titer of 1 : 320 about the fourth or fifth week.

In the spring of 1947 Q fever was clinically and serologically proved in 17 cases in Los Angeles County. Subsequently, studies of over 150 additional cases indicated that this infection is endemic in southern California (Huebner et al., 1948). Proximity to dairies by reason of occupation or residence was a common factor in the histories of more than 50 per cent. Serological surveys on 2,010 cows in the Los Angeles County area disclosed that 266 or 13 per cent possessed serum antibodies against Q fever. Not less than 12 dairies were found to have cows with positive reactions in their herds. More recently, the infection rate established by serologic tests in a dairy in Ventura County was 15 per cent. Less than 2 per cent of the

calves and bulls tested yielded serum reactions indicative of Q fever. The absence of demonstrable illness in the reacting animal and the failure to recover the rickettsia from the whole blood and blood clots suggested some local infection. Since epidemiologic data pointed to the involvement of dairies in the cases observed shortly before in man, every effort was made to obtain information on the mode of spread of the disease. Pooled specimens of flies, mosquitoes and mites, and of urine and feces from infected cows were inoculated into guinea pigs. Completely negative results were obtained. Finally, raw milk from suspected dairies was tested. Of 151 attempts by inoculating guinea pigs with the secretion, the animals became infected in 63 instances and yielded from the spleen the rickettsial organism, which by all available criteria was identified as *Coxiella burneti*. To date the milk of at least 12 dairies has been proved to be infected. The relative ease with which *Coxiella burneti* is recovered and widely distributed in southern California from milk of dairies, together with the occurrence of Q fever in the human population in the same area, suggests a causal relationship. Whether or not milk represents an effective source of infection to man, however, cannot be determined by the data thus far available. Quite recently three patients with clinical symptoms of undulant fever and a history of heavy consumption of raw milk, although serologically negative for *Brucella abortus*, furnished blood sera in which specific antibodies against Q fever were present in very high titer ($> 1:640$). Although the evidence presented by outbreaks in packing houses, stockyards and laboratories incriminated the pulmonary route of infection, clinical and epidemiological data recently unearthed reveal some similarity to those which have collected concerning undulant fever. As soon as an adequate supply of strongly reactive antigens is obtainable, it is imperative that sera in all cases in which brucellosis is suspected be tested for Q fever antibodies. Extensive studies now in progress in California will doubtless help to clarify the problem of Q fever. In this connection, it may be mentioned that an incomplete serological survey by Shepard showed Q fever antibodies had been produced in cows in many Western states. Preliminary investigations lend encouragement that the spread of the infection may be at least partially checked. Pasteurization, by the flash method at 160° F., apparently destroys the *Coxiella burneti*. Furthermore, immunological protection may be given to exposed workers in laboratories, slaughterhouses and dairies by means of recently developed yolk sac formalinized vaccines prepared by methods similar to those used in the commercial manufacture of epidemic typhus vaccine. These antigens in single-dose injections elicit specific complement-fixing antibodies in human beings. No opportunity has been afforded to obtain information on the resistance of those vaccinated to infection with Q fever (Smadel et al., 1948). Nothing is known concerning the mode of infection and pathogenesis of *Coxiella burneti* infection in cattle. Consequently, plans for the control must be deferred until this information is available.

In man's environment, then, there exists a complex host-parasite relationship between animals and various infective organisms. Because the effects of human entrance into the infection chain, as suggested throughout this review, are in many instances undesirable and because the means of avoiding it are as yet known in too few instances, efforts must be continued to increase knowledge of preventing, recognizing and treating these accidental infections. Meanwhile, it is important that all available information be effectively used.

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CASE REPORTS

ACUTE IDIOPATHIC HYPOPROTHROMBINEMIA, RESPONSE TO MASSIVE DOSES OF VITAMIN K*

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IN 1941 Rhoads and Fitz-Hugh [1] described the first case of hypoprothrombinemia in which the previously accepted causes of vitamin K deficiency, i.e., liver damage and impaired intestinal absorption, seemed to play no major rôle. Thus, they established a new subgroup of the hemorrhagic disorders, namely, idiopathic hypoprothrombinemia. Since then, several similar cases [2, 3, 4, 5, 6, 7, 8] have been reported, differing somewhat from one another, but all with a prolonged prothrombin time. The present case report is added to the small group already in the literature because of the dramatic response to large doses of vitamin K.

CASE REPORT

The patient, a 43 year old white, married housewife, was essentially well until July 1, 1947 when she first noticed the appearance of "black and blue spots" on the arms and legs. The size and number of these ecchymoses rapidly increased and on July 3, 1947, she began to bleed from the mouth and gums, associated with the sudden development of an extensive extravasation of blood into the soft tissues of the ventral surface of the tongue and the entire anterior part of the neck. The same evening, the patient noticed gross blood in the urine. Because of increasing respiratory distress and laryngeal stridor, she was admitted to the hospital shortly after midnight July 4, 1947.

The past history revealed no similar episodes, in fact, she had never noticed any tendency to bruise before. Her menstrual periods had been normal until four years previously when one ovary and part of the other had been removed because of cystic degeneration. Following this procedure menses occurred every one to three months, and were never excessive until her last period (beginning May 30, 1947) which lasted seven days and was quite profuse.

During the preceding eight years, the patient had been bothered intermittently by aching pain in the left upper thigh, a complaint for which she had seen many physicians. Numerous diagnostic surveys were carried out without attaining a satisfactory etiologic explanation and finally in 1945, the left femoral triangle was explored, no abnormalities being found. Routine hematologic studies at this time were within normal limits (table 1). During the four weeks prior to the present

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hospital entry, her family physician had advised her to take empirin compound * with one-half grain codeine three times daily for a recurrence of the pain in the left thigh. This medication was taken fairly regularly and was the only drug taken prior to the onset of her present illness.

The family history was negative for a hemorrhagic diathesis and the patient's 8 year old daughter had never shown any bleeding tendencies.

Physical examination showed a well developed and well nourished female of stated age in severe respiratory distress. Her respirations were 30 per minute, the tachypnea being associated with laryngeal stridor, the pulse rate 100 per minute and the blood pressure 130 mm. Hg systolic and 70 mm. diastolic. The skin was pale and cool, and over the extremities there were numerous ecchymotic areas. Extensive hemorrhage into the subcutaneous tissues of the neck anteriorly and laterally had produced marked swelling and discoloration giving the patient a "bull-neck" appearance. There was marginal oozing of the gums and a sublingual extravasation of blood about the size of a golf ball had forced the tongue back and upwards against the roof of the mouth and naso-pharynx causing considerable discomfort. This and the swelling in the neck were undoubtedly responsible for her respiratory difficulties, since the cardiac examination was negative and the lung fields were clear. The liver and spleen were not palpable and there were no abdominal masses or tenderness. A blood count performed shortly before she entered the hospital showed a hemoglobin

TABLE I

	1944 Sept. 26	1945 Feb. 8	1947 July 3	July 4	July 5	July 6	July 7
Hgb.	13.5 gm.	13.3 gm.	11.0 gm.	8.2 gm.	9.2 gm.	8.7 gm.	11.2 gm.
RBC	4.31 M	4.52 M	3.40 M	2.78 M	3.12 M	2.90 M	3.76 M
WBC	6750	8600	9250	19,600	—	11,400	12,400
PMN	41F 54 13NF	66F 77 11NF	79F 98 19NF	—	—	90	77
E	—	—	—	—	—	1	7
B	1	3	—	—	—	—	2
L	36	14	2	—	—	9	14
M	9	5	—	—	—	—	—
Prothrombin time	—	—	—	4 min. 25 sec. (control: 16.5 sec.)	1 min. 6 sec. (control: 17 sec.)	43 sec. (control: 15 sec.)	—
Platelets	—	—	200,000	243,000	—	—	—
Bleeding time	—	—	—	6 min.	—	—	—
Clotting time	—	—	—	13.5 min.	—	—	—
Clot retraction	—	—	—	Began in 3 hrs. Complete 24 hrs.	—	—	—
Blood chemistry	—	—	—	—	—	—	Plasma prot. 6.5 gm. N.P.N. 31 mg.
Icterus index	—	—	—	—	—	—	—
Transfusions whole blood	—	—	—	500 c.c.	500 c.c.	500 c.c.	—
Hykinone I.V.	—	—	—	280.4 mg.	72 mg.	72 mg.	72 mg.

* Empirin compound contains aspirin 3½ grains, caffeine ½ grain and phenacetin 2½ grains.

TABLE I (*Continued*)

	July 8	July 9	July 10	July 11	Aug. 5	Oct. 18
Hgb.	—	13.8 gm.	14.7 gm.	—	13.8 gm.	14.3 gm.
RBC	—	4.2 M	4.47 M	—	4.16 M	4.15 M
WBC	—	—	6000	—	6950	9100
PMN	—	—	56	—	65	68
E	—	—	2	—	6	1
B	—	—	—	—	6	—
L	—	—	42	—	23	30
M	—	—	—	—	—	1
Prothrombin time	33 sec. (control: 15 sec.)	—	24 sec. (control: 16.5 sec.)	—	23.5 sec. (control: 20 sec.)	17 sec. (control: 18 sec.)
Platelets	—	—	291,000	—	246,000	251,000
Bleeding time	—	—	—	1 min.	2 min.	2 min.
Clotting time	—	—	—	5 min.	3½ min.	5 min.
Clot retraction	—	—	—	Began in 2 hrs. Complete 18 hrs.	Began in 30 min. Complete 4 hrs.	Began in 1 hr. Complete 4 hrs.
Blood chemistry	—	—	—	Album.: 3.63 gm.% Glob.: 2.08 gm.%	Album.: 4.22 gm.% Glob.: 3.11 gm.%	Plasma Prot. 6.21 gm.% Album.: 4.1 gm. Glob.: 2.1 gm.
Icterus index	—	—	—	5 units	7 units	5 units
Transfusions whole blood	500 c.c.	—	—	—	—	—
Hykinone I.V.	72 mg.	4.8 mg.	4.8 mg.	4.8 mg.	—	—

of 11 grams, the red blood cell count was 3.4 million, white blood cell count 9250, with 77 per cent neutrophiles, 21 per cent lymphocytes, and 2 per cent monocytes. The platelet count was 200,000.

The immediate problem was the respiratory distress. Tracheotomy or laryngeal intubation was seriously considered.* Because of the danger of further hemorrhage attendant upon the former procedure and the practical impossibility of the latter and the fact that despite the laryngeal stridor there seemed to be a fairly adequate airway, it was decided to place the patient in an oxygen tent. Following this and sedation with dilaudid, the patient soon became more comfortable and an intravenous infusion of 5 per cent glucose in 1000 c.c. of Ringer's solution containing 200 mg. of ascorbic acid and 4.8 mg. of Hykinone † was administered slowly. During the night she passed a large, soft, black stool which gave a positive guaiac test.

In the morning the patient seemed considerably improved and her breathing was easier except for mucous collections in the throat. This was relieved and seemed to be controlled by atropine sulfate 1/200 gr. p.r.n. After the completion of blood studies, another infusion of 5 per cent glucose in Ringer's solution was given with 200 mg. of ascorbic acid and 4.8 mg. of Hykinone. The hematologic examination now showed 8.2 grams of hemoglobin, red blood cells 2.78 million, white blood cells 19,600 with 98 per cent neutrophiles, and 2 per cent lymphocytes. The platelet count

*The authors are indebted to Dr. Lewis F. Morrison for his advice in the management of the case from this standpoint.

†Hykinone, menadione bisulfate, Abbott.

was 243,000; the prothrombin time (Quick's method) 4 minutes, 25 seconds (control 16.5 seconds). The clotting time (capillary tube method) was 13½ minutes, the bleeding time (Duke's method) 30 minutes. It was noted that blood was still oozing from the site of venipuncture performed eight hours before. A transfusion of 500 c.c. of whole citrated blood was given and large doses of Hykinone were then administered intravenously, 72 mg. every four hours until the prothrombin time was 1 minute, 6 seconds (control 17 seconds) 24 hours later. At that time, 280.4 mg. of the drug had been given intravenously.

On July 5, 1947 another transfusion of 500 c.c. of whole citrated blood was given and it was decided to give 72 mg. of Hykinone daily until the prothrombin time approximated the normal. Demerol in 100 mg. doses was given intramuscularly to control pain and restlessness.

On the following day, July 6, the patient expectorated a few dark red blood clots and passed some bloody urine. After this, there were no further bloody stools, urine or expectoration and there was no further evidence of fresh subcutaneous hemorrhages; in fact, she was definitely improving. The prothrombin time was now 43

FIG. 1. Appearance of patient four days after onset of illness (July 8, 1947).

seconds (control 15 seconds). Another transfusion was given, although it was possible for the patient to swallow small amounts of liquids and soft foods. Supplemental therapy included multivitamin tablets, ferrous gluconate and crude liver extract intramuscularly. On July 7, her temperature rose to 103° F. but since no evidence of infection could be found (blood culture negative), this was assumed to be due to the resorption of blood in the tissues. The plasma proteins on this date were 6.5 grams per 100 c.c. Although a possible azotemia was considered, the blood non-protein nitrogen was 31 mg. per cent. The blood Wassermann and Kahn tests were negative. The patient was now comfortable without the oxygen tent and on July 8, another transfusion was given although the prothrombin time was now 45 per cent of normal. The following day the red cell count was 4.2 million, and the hemoglobin was 13.8 grams. The dose of Hykinone was then reduced to 4.8 mg. daily and finally discontinued two days later when the prothrombin time was 24 seconds (control 16.5 seconds). By July 11, the patient was well enough to sit in a chair and on July 12, she was discharged from the hospital to convalesce at home. The total dose of Hykinone administered intravenously over a period of eight days was 585.6 milligrams.

While at home, the patient was advised to continue with oral multivitamin therapy and ferrous gluconate and was given intramuscular injections of crude liver extract intramuscularly twice weekly by her family physician. She received no further vitamin K therapy. She was seen again on October 18 at which time she reëntered the hospital because of pain in the left hip region. Roentgen-ray studies showed calcification in the bursa overlying the greater trochanter of the left femur. The blood studies were repeated at this time and all were within normal limits (table 1). The prothrombin time was 17 seconds (control 18 seconds). Her symptoms were attributed to a chronic tendinitis of the left gluteus medius with calcification and secondary bursitis. This impression was confirmed at operation on October 28, 1947. It was felt that these findings were responsible for the symptomatology in the left hip region and thigh for the preceding eight years.

Discussion

The fulminating onset and dramatic recovery in this case have no parallel in the previously recorded cases of idiopathic hypoprothrombinemia. The only case which approached this one in rapidity has been described by Austin and Quastler,[7] but their patient had had periodic bleeding episodes over a period of several months and the autopsy findings showed widespread granulomatous lesions. These two cases are the only ones to which the term "acquired" might possibly be applied since, as may be seen in table 2, almost all of the other patients showed pathological bleeding tendencies early in life, lasting a few months to several years. All were males and were considered to have a congenital and/or hereditary background. Murphy and Clark,[4] Heinild [5] and Giordano [3] mention female siblings afflicted with bleeding tendencies but quote no complete studies.

The response to therapy was no less remarkable than the clinical picture on entry. We frankly did not expect the patient to survive and since the platelet count was normal and the prothrombin time had not yet been determined, the Hykinone and ascorbic acid were given empirically, yet the former none the less fortuitously in retrospect. Six hours after entry when the prothrombin time was found to be 4 minutes, 25 seconds (control 16.5 seconds) (after 4.2 mg. of Hykinone intravenously), it was decided to administer large doses of Hykinone intravenously without delay. Whether or not such tremendous doses were actually necessary is now a matter of speculation. It is quite possible that smaller amounts of the drug may have been as effective. Quick [8] and Fashena and Walker [9] described instances of low prothrombin concentrations, 8 per cent and 40 per cent respectively, responding to small doses of vitamin K, 30 mg. and 4 mg. Lucia [29] believes that in hypoprothrombinemia hemorrhagic phenomena only occur when the prothrombin concentration falls below 10 per cent. Aggeler et al.[10] report a case of hypoprothrombinemia due to exogenous dietary deficiency in which the prothrombin concentration (Quick) rose from 10 per cent to 55 per cent in 24 hours, after 5 mg. of synthetic vitamin K intravenously. However, the urgency of the situation and the relatively low toxicity of the drug seemed to justify our decision at the time. Only after the first 24 hours when oozing from the various sites of venipuncture had cleared and the prothrombin time was 1 minute, 6 seconds (control 17 seconds) did we feel safe in decreasing the dose of Hykinone. The rapid improvement in this case has been attributed primarily to Hykinone, yet the importance of the blood transfusions cannot be minimized.

TABLE II

Source	Age of Onset	Duration	Course	Sex	Family History	Prothrombin Evaluation	Coagulation Time	Clot Retraction	Bleeding Time	Tourniquet Test	Platelets	Fragility Test	Remarks
Rhoads and Fitz-Hugh, 1941	9 mos.	18 yrs.	Fatal	M	None	70 sec. to 120 sec. (Normal: 23 sec.) No response to vitamin K plus bile salts.	8–360 min.	Normal to poor	1–25 min.	Positive	140,000 to 416,000	—	Normal liver function tests. Calcium 9.8 to 10 mg.%. No excess antithrombin or antiprothrombin. Qualitative defect in fibrinogen. Autopsy revealed some atrophy of "liver columns" but inadequate to explain low prothrombin level.
Beard (Quoted by Quick), 1942	Birth	9 yrs.	Chronic	M	None	Prothrombin concentration 25% of normal. Intensive vitamin K therapy elevated it to 75%. Poor response to fresh whole blood transfusions.	Delayed	—	Not prolonged	—	Normal in number and quality	—	Original diagnosis—hemophilia.
Giordano, 1943	5 yrs.	17 yrs.	Chronic	M	Mother, father, brother, sister, with low prothrombin concentrations.	Prothrombin time (Quick) 210 sec. (normal 25 sec.) No response to vitamin K or parenteral liver extract. Plasma produced temporary rise to concentration 40% of normal.	4–6½ min.	Good	4–7½ min.	Positive	312,000	—	Liver function normal although serum proteins 5.4 gm.%. Low blood ascorbic acid (0.48 mg.%) which responded to cevitamic acid. Calcium 9 mg.%. Serum proteins low (5.34 to 5.9 gm.) in entire family.
Murphy and Clark, 1944	4 yrs.	14 yrs.	Chronic	M	Sister died at age of 4, "splenic anemia."	Prothrombin time (Quick) 60 sec. to 100 sec.—normal 16 sec. Resistant to vitamin K and bile salts. Bleeding temporarily controlled by whole blood only.	3–10 min. Normal	Good	1½–12 min.	Negative	113,600 to 358,000	Hemolysis began 0.45—ended 0.32.	Liver function tests normal; spleen slightly enlarged. Calcium 9.8 mg.%; blood ascorbic acid 1.5 mg.%. Fibrinogen (331 mg.%) normal but with qualitative defect. No excess antithrombin or antiprothrombin. Nail-bed capillaries abnormal as in pseudohemophilia.

TABLE II (*Continued*)

Source	Age of Onset	Duration	Course	Sex	Family History	Prothrombin Evaluation	Coagulation Time	Clot Retraction	Bleeding Time	Tourniquet Test	Platelets	Fragility Test	Remarks
Heinild, 1944 (a)	7 days	3¼ yrs.	Chronic	M	Maternal aunt with hypoprothrombinemia. Uncle with bleeding tendency. Brother (see below).	Prolonged prothrombin time	—	—	—	—	73,000	—	Also fibrinopenia (0.14 gm.%); transitory thrombocytopenia.
(b)	7 days	2 yrs.	Chronic	M	Brother to above	Prothrombin time 120 sec. Normal 18-20 sec. (Larsen and Plum). Responded to transfusions.	—	—	—	—	20,000 to 159,000	—	Fibrinopenia (0.057 gm.%). Bone marrow rich in cells with considerable lymphocytosis and reduced erythropoiesis.
Hauser, 1945	14 days	5 yrs.	Chronic	M	Brother with prothrombin concentration—53%.	Prothrombin concentration 25% to 65% of normal. No response to vitamin K. Slight response to transfusions of whole blood.	3 min. 7 sec. to 11 min. 20 sec.	Good 20–60 min.	2 min. to 3 min.	Negative	238,000 to 716,000	—	Liver function tests normal. Calcium 11.6 mg.% Fibrinogen 0.34 gm.%. No increase in antithrombin.
Austin and Quastler, 1945	56 yrs.	10 mos.	Fatal	M	None	Prothrombin concentrations from 6% to 90% of normal. Resistant to vitamin K, bile salts and all other therapy.	—	Very	1 min. 15 sec. to 4 min.	Negative	198,000 to 277,000	Normal	Autopsy: Widespread granulomatous lesions, ? T.B., Hodgkin's sarcoma or sarcoidosis. Moderate liver damage. No excess antithrombin or antiprothrombin. Fibrinogen 0.63 gm.%. Calcium 9.4 mg.%.
Quick, 1946	Unknown	22 yrs.	Chronic	M	Mother and sister with prothrombin concentration around 50%.	Prothrombin concentration 35% to 50% of normal. No response to vitamin K.	—	—	—	—	—	—	Hypoprothrombinemia discovered accidentally; no history of pathologic bleeding. "Probably congenital and hereditary."

The seriousness of the patient's condition, however, would not have permitted an attempt at treatment with vitamin K alone. According to Aggeler,[11] one blood transfusion might possibly have raised the prothrombin concentration to 12 per cent, but rather certainly not to 25 per cent. The ascorbic acid obviously did not affect the prothrombin time. Even in dicumarol poisoning the use of large doses of Hykinone alone has not been considered a complete substitute for blood transfusions. In fact, the similarity between the clinical picture in this case and that seen following dicumarol overdosage strongly influenced our giving large doses of vitamin K. The marked improvement in this patient following Hykinone is in contrast to the lack of response to this drug in the majority of previously reported cases.

No satisfactory explanation for the hemorrhagic phenomena in this patient is offered. Her otherwise healthy appearance and total lack of gastrointestinal symptomatology would seem to rule out faulty absorption. It was felt that diffuse hepatic disease was not likely since the total plasma proteins, albumin-globulin ratio, icterus index and cephalin flocculation test were all within normal limits. As a matter of fact, in this particular case one might infer that the rapid rise in prothrombin concentration following the administrations of vitamin K was in itself evidence of hepatic function that could not have been too badly impaired.

The effect of salicylates on the blood prothrombin concentration obviously cannot be ignored since the patient had been taking empirin compound regularly over a period of several months, yet the daily dose of aspirin did not amount to more than 10 to 15 grains. Link et al.[12] found salicylic acid to be one of the end products in the breakdown of dicumarol and later showed that in rats on a low vitamin K diet, a single dose of salicylic acid induced temporary hypoprothrombinemia. Coombs et al.[13] in a series of 17 rheumatic fever patients and Butt et al.[14] in a similar series of 50 patients, all taking moderate to large doses of sodium salicylate (6 to 10 grams daily), reported a definite, but only moderate, drop in prothrombin time after administration of the drug for four days or more; a drop insufficient to cause spontaneous bleeding. Fashena and Walker[9] produced experimentally a prolongation of the prothrombin time on the second day of salicylate administration, but a spontaneous return to normal ensued in the face of continued medication. Similar results have been described by Meyer and Howard[15] and Rapoport, Wing and Guest.[16] Petechial hemorrhages due to thrombocytopenia attributable to salicylate administration have been reported,[17, 18] as well as frank purpura,[18, 19] but no blood studies were carried out in the latter instances. Ashworth and McKemie[20] have attributed two deaths to salicylate poisoning. These cases showed very extensive petechial hemorrhages at autopsy, which the authors concluded were due to capillary damage and hypoprothrombinemia but no antemortem hematologic studies had been carried out.

It would appear from the current literature that salicylates may definitely lower the prothrombin concentration, but we have seen no report, either clinical or experimental in which salicylates produced a hypoprothrombinemia associated with almost fatal hemorrhagic phenomena. If salicylates are to be held accountable in this case, it must be assumed that the patient suddenly developed an idiosyncrasy to the drug, not unlike anaphylaxis, in which the ability of the liver to synthesize prothrombin was seriously impaired.

Summary

1. A case of so-called idiopathic hypoprothrombinemia successfully treated with large doses of vitamin K is described.

2. The influence of salicylates on prothrombin time is discussed.

3. Previously reported cases of idiopathic hypoprothrombinemia and their points of difference with this case are discussed.

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POTASSIUM DEFICIENCY ASSOCIATED WITH DIABETIC ACIDOSIS *

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The clinical syndrome relative to an abnormally low concentration of serum potassium has been definitely associated with certain cases of diabetic acidosis.

Three cases of hypopotassiumemia following diabetic acidosis have been reported, one case by Holler [1] and two cases by Nicholson and Branning.[2] In these three cases there was good response to therapy of the acidosis, only to be followed shortly by generalized muscular weakness accompanied by progressive respiratory difficulty. In each case the potassium concentration of the serum was found to be decreased and in the two cases which received potassium the clinical response was striking. The third patient received no potassium and died in collapse 37 hours after admission, although the blood sugar and serum carbon dioxide combining power had been normal for 12 hours.

Nicholson and Branning suggest that five deaths in the Duke Hospital acidosis series were due to potassium deficiency although no laboratory determinations of potassium had been performed.

In presenting this case, we wish also to suggest that the syndrome of potassium deficiency following diabetic acidosis occurs more frequently than is sus-

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pected and that its recognition may bring about a notable decrease in the present mortality rate in diabetic acidosis.

It is not the purpose of this paper to present a review of potassium metabolism. However, it is necessary to describe a few of the concepts of potassium metabolism which are pertinent to the case presented.

Potassium is the major base of intra-cellular elements, and plays the rôle of counterpart to extra-cellular sodium. Potassium within the cells serves the same general functions relative to osmotic pressure regulation and acid-base balance as does sodium in extra-cellular fluids. The normal serum potassium level ranges between 16 and 22 milligrams per 100 c.c. of serum.

It is generally accepted that potassium ions play an important part in the transmission of nerve impulses and in synaptic transmission. Opinions upon the exact functions of potassium in these respects are still controversial. It is probable that the deficiency of potassium within and about motor nerves produced the picture of muscle fatigue encountered in the reported cases and in our study.

Allott and McArdle [3] in a study of three cases of periodic familial paralysis showed that attacks of paralysis, clinically identical with a natural attack, would be produced by the administration of glucose by mouth, by insulin, and more consistently by glucose and insulin together. Weakness developed when the potassium level of the serum reached 12 milligrams per cent and the complete picture of severe generalized muscle weakness appeared at a concentration of 10 milligrams per cent. All three cases of periodic familial paralysis responded to potassium chloride orally. Potassium balance experiments disclosed that potassium was not lost through diuresis but that probably it entered the tissues. Allott and McArdle believe that in this disease there exists a periodically increased demand for potassium by the muscles. The body attempts to gratify this demand by withdrawing potassium from the serum and by diminishing the excretion of potassium.

Fenn [4] showed that potassium is an especially mobile element within the body. Acid-base imbalances cause shift of potassium ions in or out of cells. Potassium migrates from cells to plasma in conditions involving an excessive excretion of sodium chloride and water. Thus, diabetic acidosis, as well as the parenteral administration of large quantities of glucose solution are two conditions causing this shift of potassium from intra-cellular spaces to plasma. Fenn also contends that the deposition of water and potassium within the liver cells is a prerequisite of glycogenesis, indicating that during the treatment of diabetic acidosis potassium would be withdrawn from the plasma and deposited in the liver.

Castleden [5] concluded that three methods of decreasing serum potassium concentration are administration of glucose, injection of insulin and injection of adrenalin. With the administration of glucose and insulin he associated the decrease of serum potassium concentration with the passage of sugar from blood into tissues.

Atchley, Loeb and associates,[6] in studies upon the withdrawal and reëstablishment of insulin in diabetic patients, drew the following conclusions. During initial glycosuria, preceding development of acidosis, there occurs a loss of intracellular and extra-cellular body fluids accompanied by their constituent electrolytes. The excretion of water and electrolytes tended to seek a level during the pre-acidosis glycosuria stage. As ketogenic acidosis developed a secondary in-

crease in excretion of water and electrolytes occurred, which continued until the acidosis was terminated by treatment. In the recovery state, after reëstablishment of insulin, there was retention of intra-cellular and extra-cellular water and electrolytes.

Case Report

H. C., 51 year old female, was admitted to Mount Carmel Mercy Hospital at 3:30 a.m., August 20, 1947, in coma. History obtained from relatives disclosed that five months prior to admission the patient first noticed weight loss, which progressed to a total loss of 45 pounds from an original weight of 155 pounds. The weight loss was accompanied by polydipsia, polyphagia and a mild degree of polyuria. Three weeks prior to admission she consulted her physician and the diagnosis of diabetes mellitus was made. Hospitalization was urged at this time but refused by the patient, who also made little effort to adhere to her diet. Ten days prior to hospital admission, dyspepsia was noted, accompanied by a foul taste in the mouth, anorexia, and more severe polydipsia. On the evening preceding admission, the patient became stuporous and lapsed into coma at 11:00 p.m. There was no history of the patient ever having received insulin.

Physical examination at the time of admission revealed the patient to be in coma, but responsive to painful stimuli. Kussmaul breathing was evident and a definite odor of acetone was on the breath. There was a slight decrease of the intra-ocular pressure. The pupils were equal, of normal size and reactive to light. Corneal reflexes were present but sluggish. The skin was dry, the extremities cool. Temperature taken rectally was 99° F. Pulse rate was 140, regular and rhythmic. The blood pressure was 115 systolic, 70 diastolic. The heart and lungs were normal to auscultation and percussion. The abdomen and extremities were negative. There was a generalized hyporeflexia with no pathologic reflexes present. A catheterized urine specimen was strongly positive for sugar and acetone. The diagnosis of diabetes mellitus with acidosis and coma was made. Treatment was begun immediately, and consisted of the following: (1) Regular insulin, 25 units intravenously, 50 units subcutaneously. (2) One-sixth molar racemic sodium lactate, 1000 c.c., intravenously. (3) Indwelling catheter, urinalysis for sugar and acetone performed at half-hour intervals. (4) Regular insulin, 25 units subcutaneously at half-hour intervals until urine became acetone free. (5) Glucose, 5 per cent in saline, intravenously, continuously, until the patient was able to take fluids by mouth. Five hundred cubic centimeters of 10 per cent glucose in saline was given when the glycosuria decreased in the presence of persistent severe acetonuria. (6) Nasal oxygen. (7) External heat. (8) Gastric lavage with 5 per cent sodium bicarbonate solution, 250 c.c. of which was left in the stomach.

The patient regained consciousness at 6:15 a.m., three hours after admission, after having received 175 units of regular insulin. At this time the respiratory rate was 34 per minute, pulse 140, blood pressure 120 mm. Hg systolic, 75 diastolic. Kussmaul type of respirations persisted. Nasal oxygen was discontinued and the patient was placed in an oxygen tent.

At 8:15 a.m., by which time 275 units of insulin had been administered, the blood sugar was 376 milligrams per cent, the serum carbon dioxide combining power 25 volumes per cent. By 11:00 a.m., seven and one-half hours after admission, the blood pressure had dropped to 90 systolic, 60 diastolic, pulse rate was 88 per minute. Kussmaul respiration had ceased, and, although there was no objective evidence of labored breathing, the patient complained of respiratory distress and generalized weakness and requested to remain in the oxygen tent. Physical examination revealed no evident cause of the respiratory difficulty or of the weakness. At this time the

blood sugar was 356 milligrams per cent and the serum carbon dioxide combining power 37 volumes per cent. During these seven and one-half hours the patient had received 400 units of insulin, three liters of fluids parenterally and approximately one liter orally (figure 1).

Impairment of respiration gradually increased despite the administration of eight liters of oxygen per minute. The blood pressure remained in the vicinity of 90 systolic, 60 diastolic. By 6:00 p.m., 14 hours after admission, the patient had received 635 units of insulin and approximately six liters of fluids. Acetone was no longer present in the urine. At this time the serum potassium, as determined by the method of Kolmer and Boerner, was reported as 10 milligrams per cent, which is well below the minimum normal level.

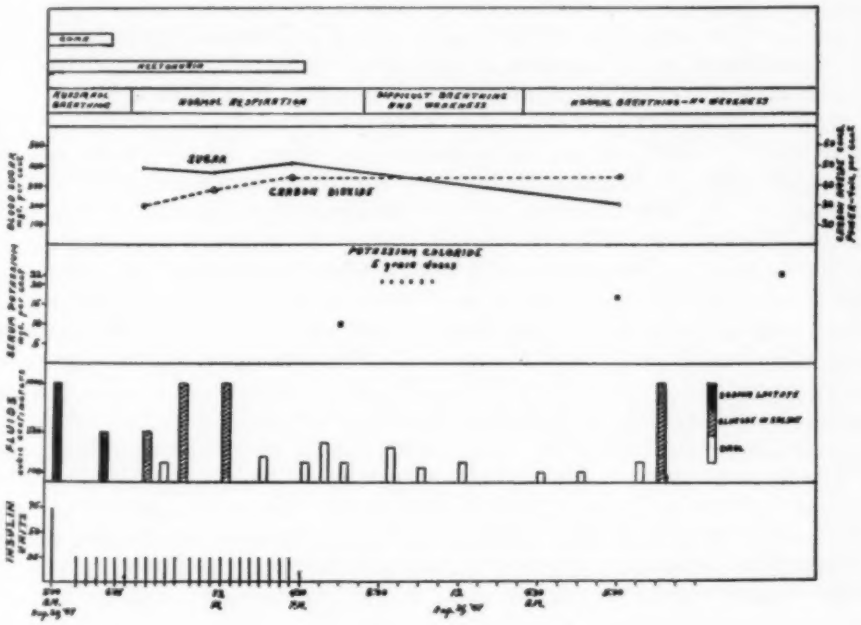

FIG. 1.

Potassium chloride was administered in five grain doses at half-hour intervals for six doses. Shortly after receiving the total dosage, the respiratory impairment was noticeably diminished and progressive improvement ensued. At 10.00 a.m., August 21, thirty-six hours after admission, the serum potassium level was 16 milligrams per cent, the lower limit of normal. The muscle weakness and respiratory distress had disappeared and the patient no longer needed oxygen.

Recovery thereafter was uneventful and the patient's diabetes was controlled. Later serum potassium levels were well within normal range.

Apparently several factors entered into the reduction of serum potassium in this previously untreated diabetic patient. These are: (1) Excretion of potassium accompanying extended glycosuria before the development of acidosis. (2) Increased potassium excretion during development of acidosis. (3) Loss of potassium by diuresis with copious amounts of fluid, five liters during 14 hours of treatment. (4) Withdrawal of potassium from serum and deposition

of the potassium in liver cells, caused by the administration of 635 units of insulin during treatment. (5) Relative decrease due to hemo-dilution with fluids.

In cases thus far reported, potassium deficiency associated with diabetic acidosis was recognized in the post-coma stage. It is not unreasonable that, in severe cases, it may develop and be the unsuspected cause of death during coma.

Case histories of diabetic deaths at Mount Carmel Mercy Hospital during the past eight years were reviewed. There were 25 cases in which acidosis of some degree was present although not the actual cause of death in the majority. In five cases there was suggestive evidence that the actual cause of death may have been potassium deficiency. Three of these cases exhibited favorable response to treatment of the acidosis, but collapse and death nevertheless ensued. Although no laboratory determinations of serum potassium had been performed, the clinical picture in these cases was strongly suggestive of potassium deficiency.

We believe that the recognition and treatment of potassium deficiency will play an integral part in decreasing the mortality rate in diabetic acidosis.

Potassium inhibition of the heart is known to occur when the heart is perfused with a solution containing potassium in excess, or potassium unaccompanied by calcium. The effect consists of a gradual increase of the duration of diastole until the heart comes to rest in a completely relaxed state.[7] Death from cardiac failure results when the serum potassium reaches a concentration four times its normal. Potassium ions are toxic when administered intravenously in high concentration. But there is no danger in the injection of potassium in concentrations normally characteristic of extra-cellular fluid. The potassium ions, if in excess, are rapidly excreted. However, where renal function is severely impaired, caution must attend the administration of potassium by any route. Large amounts of potassium have been administered orally without resulting in untoward reactions.[8] Potassium chloride may be given orally in doses of 5 to 10 grams in tablet form or in water. It may be injected intravenously in doses of 50 c.c. of a 2 per cent solution, taking at least ten minutes for the injection.[9] It is felt that in those cases of diabetic acidosis in which there occurs a low serum concentration of potassium the administration of the latter according to the recommended methods will not result in any degree of toxicity.

Summary

1. The syndrome of potassium deficiency has been discussed.

2. The relation of diabetic acidosis and its treatment to the production of potassium deficiency has been described.

3. A case of potassium deficiency associated with diabetic acidosis has been presented and its treatment and results described.

4. The recognition of this syndrome may be of definite aid in the reduction of mortality from diabetic acidosis.

5. Potassium toxicity is mentioned, with recommendations upon dosage and precautions to attend the administration of potassium.

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PITUITARY IMPLICATIONS IN HYPERTROPHIC PULMONARY OSTEOARTHROPATHY *

By William Bloom, M.D., *New York, N. Y.*

The pathogenesis of chronic hypertrophic osteoarthropathy remains unsolved. The clinical entity is obscured rather than clarified by a multiplicity of unsatisfactory hypotheses.[1]

Within the last five or six years evidence has appeared in the literature that would seem to point to a more logical understanding of this uncommon disease. That the proper approach to this subject is an endocrine one may be suspected by emphasizing the common characteristics of three syndromes which may be confused clinically, viz.—acromegaly, pachyperiostosis of Touraine and Gallé [2] and hypertrophic pulmonary osteoarthropathy. The first condition is of definite endocrine origin. The second is very often considered of endocrine origin. The last, though frequently confused with the former, is rarely so considered. It may be conceded that anoxia [3] and toxicity are important factors, if not the only factors, in the pathogenesis of clubbed fingers, since this condition is found in the presence of advanced pulmonary disease or chronic anoxia of cardiovascular origin. On the other hand, severe hypertrophic pulmonary osteoarthropathy frequently occurs in early pulmonary disease and often even before the pulmonary pathologic process can be clinically detected. It would appear, therefore, that these two conditions represent separate entities and that a common etiology and pathogenesis is very unlikely.

Because of inadequate knowledge regarding the origin and development of chronic hypertrophic pulmonary osteoarthropathy many synonyms have arisen which presumably represent stages of one clinical entity but which in all likelihood represent several different syndromes. It is to be hoped that further knowledge will separate these entities and regroup them in proper pathologic or etiologic relationships. Thus, E. A. Locke and A. Grollman [4] list a few of the

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synonyms in vogue: (1) clubbed fingers, (2) hippocratic fingers, (3) essential dactylomegaly, (4) hypertrophic pulmonary osteoarthropathy, (5) Marie Bamberger's disease, (6) hyperplastic osteosis, (7) pachyperiostosis, etc., etc. They define the condition as being characterized by painless, general, symmetrical clubbing of the fingers and toes, often associated with hypertrophy of the long bones of the forearms and legs. Often it is secondary to some chronic disease, particularly of the lungs. Mendelowitz [5] classifies the disease from the etiological standpoint into (1) The hereditary form (a rare, primary disease passed on as a

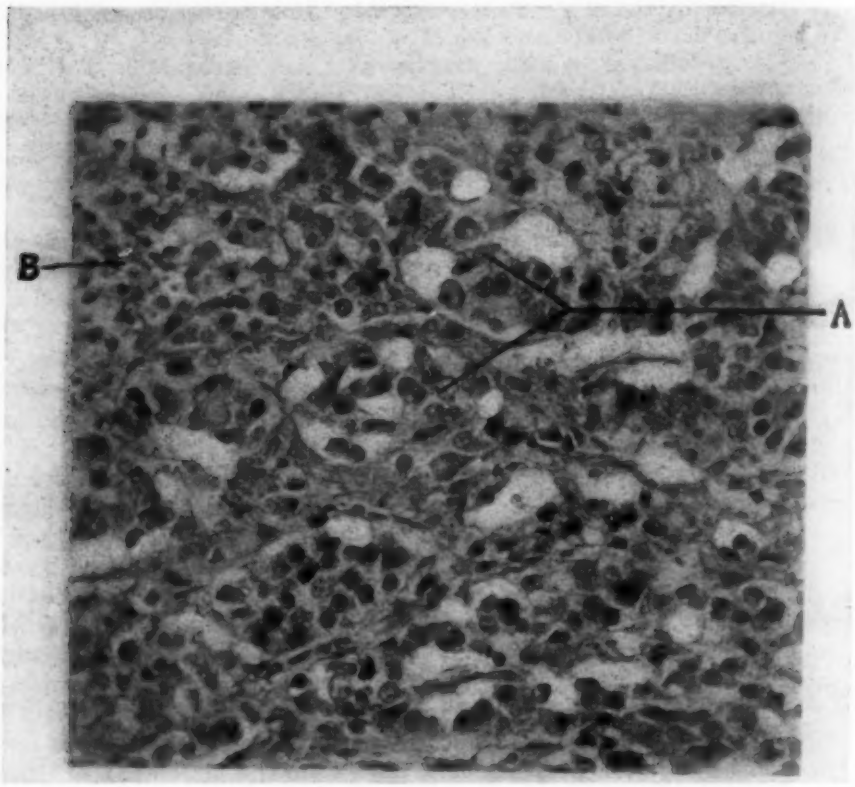

FIG. 1. Pituitary gland (× 250). Metastatic cancer at A is infiltrating the characteristic anterior lobe parenchyma (B).

Mendelian dominant type), (2) The idiopathic form in which there is no evidence of primary disease and no hereditary factor (this may be the same as that described by Touraine and Gallé), (3) The acquired form—(a) associated with pulmonary conditions such as tuberculosis, empyema, bronchiectasis, abscess, etc., (b) secondary to cardiac conditions such as congenital heart disease with cyanosis and subacute bacterial endocarditis, (c) following hypertrophic biliary cirrhosis, (d) following such gastrointestinal conditions as ulcerative colitis, dysentery, etc., (e) in association with miscellaneous diseases such as Raynaud's disease, cystopyelitis, purpura and polycythemia. Pathologically there is enlarge-

ment of the fingers and toes due to proliferation of the soft tissues and increase in thickness of the periosteum. Cyanosis of the fingers is very common. The hands may be enlarged to give the appearance of gigantism. Continuing with

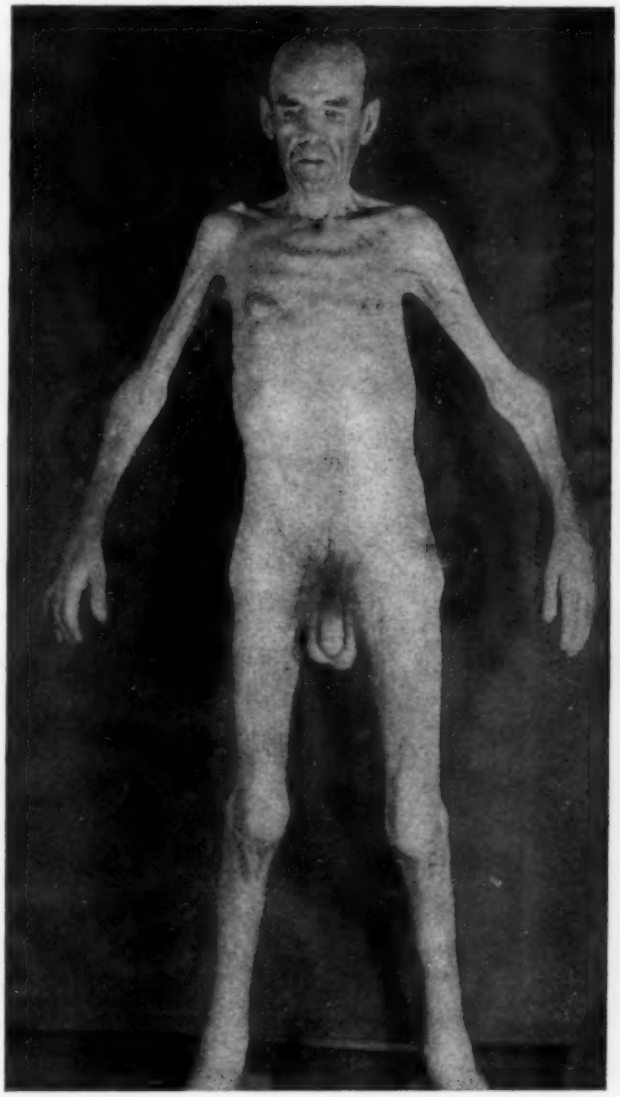

FIG. 2. Appearance of patient on second admission showing fusiform enlargement of the long bones, hypertrophy of the right breast and large, spade-like hands, not unlike acromegaly.

the description of the disease, most authors include in the same category those cases which present (in addition to the above) severe subperiosteal bony proliferation associated with ossifying periostosis of the long bones. However, as indicated, it is likely that the more severe disease bears an entirely different

etiologic relationship. From the symptomatic standpoint, Sternberg [6] classifies the disease into three types: (a) clubbing of the fingers and toes without changes in the long bones (this is the most common type, symptoms are absent), (b) Von Bamberger's type—clubbing of the fingers and toes associated with painful thickening of the long bones especially the forearms and lower legs, (c) Marie's

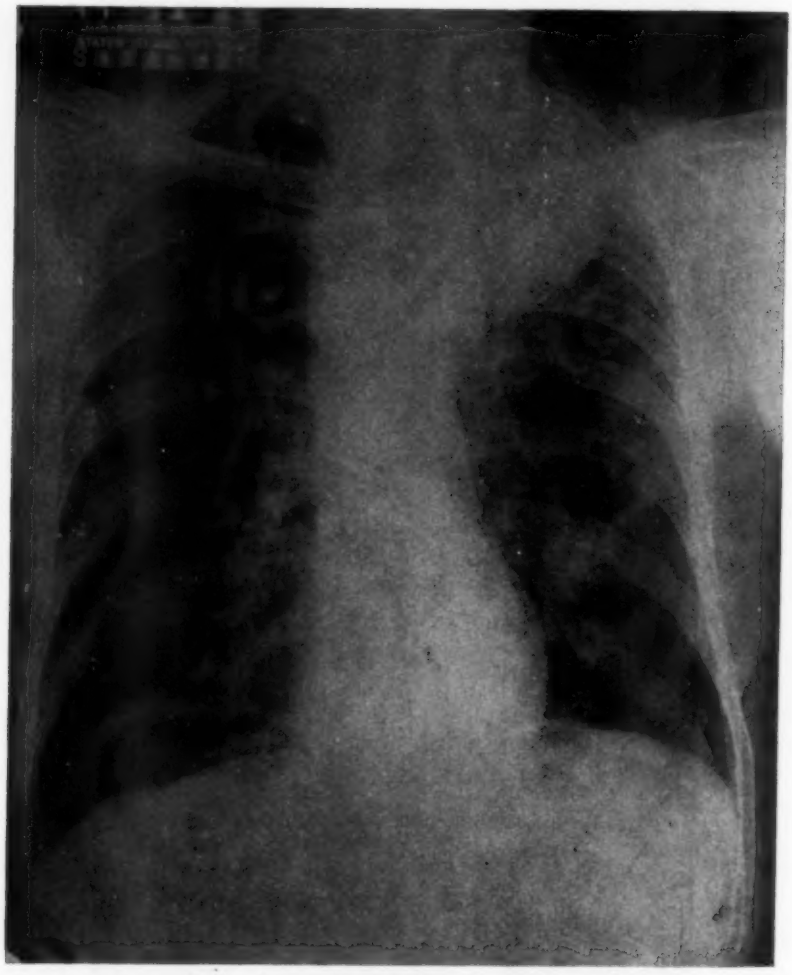

FIG. 3. Roentgenogram of the lungs showing bronchiogenic neoplasm in the apical and subapical portion of the left upper lobe with metastatic involvement of the lower lobe.

type—deformities are markedly conspicuous, severe and painful, and overshadow the primary disease found.

The trend of thought regarding the etiology and pathogenesis of this interesting syndrome has been away from existing concepts and in the direction of chemical or hormonal stimulation. In 1929 Crump [7] hypothesized "abnormal substance circulating in the blood which affects the periosteum of the bones, the joints and terminal phalanges as evidenced by clubbing of the fingers" (this could

conceivably be of hormonal origin). Tufting of the terminal phalanges of the fingers was regarded by Cushing [8] as pathognomonic of acromegaly. It is interesting to note that this finding is likewise present in hypertrophic osteoarthropathy. Forte,[9] Rogers,[10] Aschoff,[11] Fried [12] have at various times offered evidence in favor of the concept that the lungs are endowed with functions in addition to respiration suggesting a secretory action. Fried,[13] in an excellent article

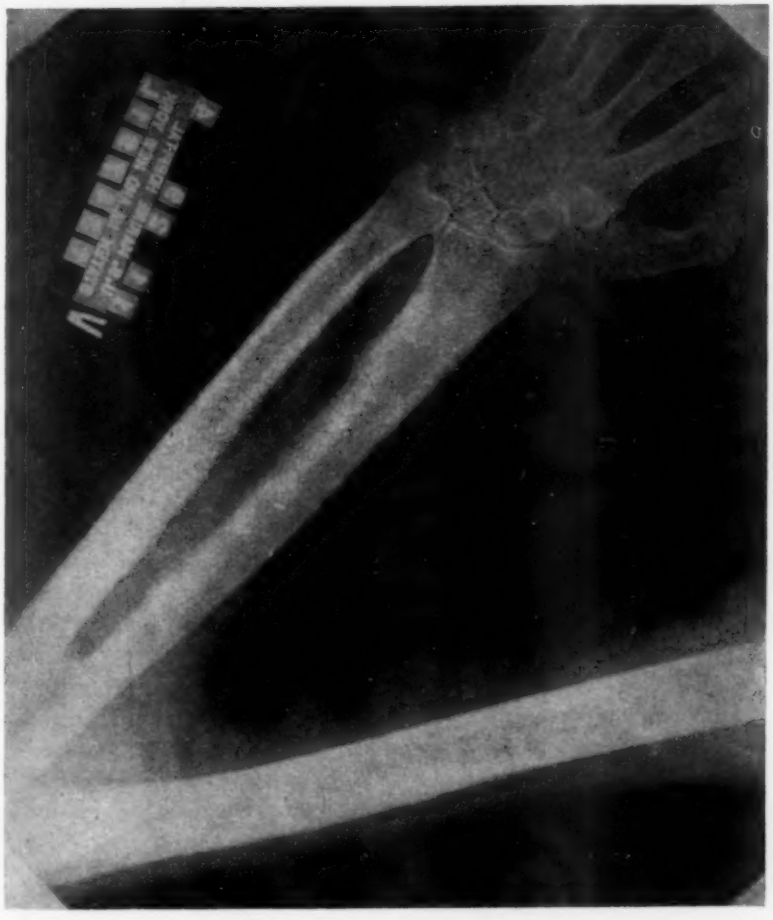

FIG. 4. Roentgenograms of the upper extremity showing ossifying periostitis with subperiosteal bone proliferation.

published in 1943, promulgates the concept that diffuse osteoarthropathy found in neoplastic disease of the lungs is in all probability caused not by toxins or circulatory disturbances but by endocrine imbalance akin to acromegaly and pachyderma with pachyperiostosis. To substantiate this hypothesis he presents three cases of chronic hypertrophic osteoarthropathy on whom autopsy revealed hyperplasia of the eosinophilic cells of the pituitary gland. He suggests the possibility that the stimulus to overdevelopment of the eosinophilic cells arose

FIG. 5. Spade-like enlargement of the hands with widening of the wrists and cylindrical deformity of the forearms.

FIG. 6. Marked cylindrical deformity of the ankles and legs.

from some endocrine factor inherent in the lungs. In the case to be presented metastasis to the pituitary gland was found. It is suggested that the metastatic lesions acted as a stimulant to excessive secretion of pituitary hormone, giving rise to the osseous syndrome in much the same manner as acromegaly. In support of this concept, attention may be called to hypertrophy of the breasts asso-

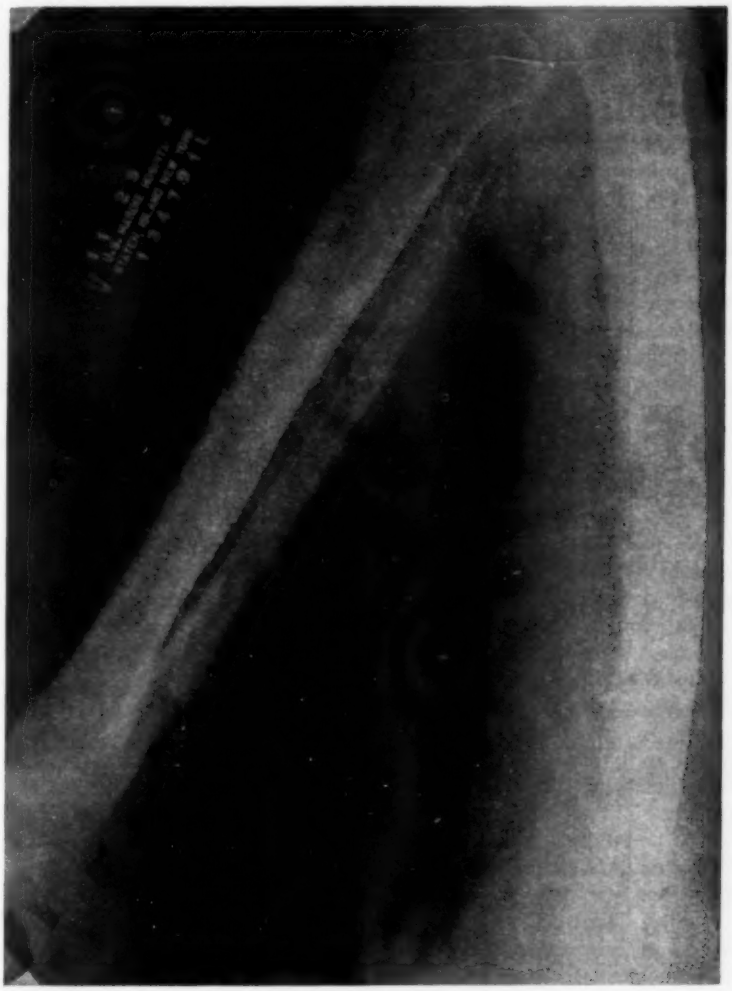

FIG. 7. Roentgenograms of the lower extremity showing ossifying periostitis with subperiosteal bone proliferation.

ciated with this disease as reported by Bamberger, Fried and present in the case to be described. In addition, Fried's case also presented multiple cysts of the adrenal cortex. Rynearson and Sacasa [14] report the condition developing in a patient operated on for hyperthyroidism. This patient developed postoperative hypothyroidism with progressive exophthalmus. There were no lung lesions. Thomas [15] described a similar case without lung lesions. Both of these cases are

FIG. 5. Spade-like enlargement of the hands with widening of the wrists and cylindrical deformity of the forearms.

FIG. 6. Marked cylindrical deformity of the ankles and legs.

in many ways similar to the syndrome described by Touraine and Gallé [2] and implicate the pituitary gland.

Case Report

The patient, a 51 year old white male merchant seaman (cook), was admitted to the Medical Service for the first time on November 5, 1943 complaining of severe pain in both hands and feet and in the left shoulder. The pain in the left shoulder radiated down the left arm. There was increasing pain and limitation of motion in the joints of both extremities. These symptoms had been present and progressive for three months and were aggravated by cold weather. There was no cough or expectoration and no marked weight loss. He stated that his fingers were large since childhood but that the joint involvement was of recent onset. One month prior to admission he became aware of painful enlargement of both breasts.

Physical examination revealed a rather well-developed and nourished white male presenting marked enlargement of all the joints with cylindrical deformity of the long bones of the forearms and legs. There was extensive clubbing of the fingers. The breasts were enlarged and tender. His general appearance was not unlike that of an acromegalic. There was profuse sweating of the hands and feet, more marked on the left side. The remainder of the physical examination was not remarkable. The lungs were negative to percussion and auscultation; no râles were heard. Urinalysis, blood count and Wassermann test were negative. Roentgenogram of the lungs revealed an homogeneous density in the left upper lobe to the left of the trachea, with some linear strands of increased density to the apex. This was interpreted as an old acid fast lesion, probably inactive. Repeated sputa examinations were negative for acid fast bacilli except on one occasion when rare acid fast bacilli were thought to be present. Following this report, however, concentrated sputa, gastric specimens and guinea pig inoculations were negative for tuberculosis. Roentgen studies of the long bones and of the hands and feet revealed evidence of far advanced hypertrophic pulmonary osteoarthropathy with periosteal thickening and beginning flexion deformities of the joints of the fingers. Roentgenograms of the skull showed no abnormality of the sella turcica. Sedimentation rates were persistently elevated. Blood uric acid was 3.8 mg. per cent; serum calcium 11 mg. per cent; phosphorus 3.8 per cent; alkaline phosphatase 3.4 Bodansky units and acid phosphatase was 1.2 Bodansky units.

His course in the hospital was slowly progressive, with weight loss and persistent, severe joint pains which were unrelieved by symptomatic therapy. He remained in the hospital for eight months during which time serial roentgenograms revealed no progression of the pulmonary lesion. He was discharged, unimproved, on August 28, 1944 but was re-admitted on October 30, 1944 in a markedly emaciated state with evidence of an early Horner's syndrome on the left side. In the interim following discharge he had developed a productive cough, increasing in intensity. He complained bitterly of joint and bone pains. A roentgenogram of the lungs on this occasion revealed marked extension of the lesion previously reported, obviously malignant. There was a chain of firm, non-movable lymph nodes in the anterior triangle of the neck. Roentgenographic studies of the long bones indicated increased periosteal thickening and subperiosteal new bone formation, greater in extent than previously reported. His course was progressively downward and he died on May 31, 1945, seven months after the second admission.

Autopsy Findings

Significant findings on postmortem examination, in addition to the pathological changes of the osseous system, were limited to the lungs and pituitary gland. The

left lung weighed 810 grams, the upper lobe was stony hard in consistency and the overlying pleura was thickened with gray fibrous tissue. The lower lobe was crepitant and revealed two small nodules, palpable deep within its substance. The cut section of the left upper lobe revealed almost complete infiltration with confluent masses of gray-black or yellow-gray tumor, irregular fibrous strands interlaced throughout. No normal parenchyma was present in this lobe. On microscopic examination several large zones of neoplastic infiltration were observed with definite acinar grouping. The cells showed a columnar pattern with clear or acidophilic cytoplasm. Nuclei were frequently of large and irregular form and pattern. The bronchial walls were invaded. There were many foci of neutrophiles in areas of necrosis and abscess formation. The peribronchial lymph nodes were heavily infiltrated by masses of tumor cells.

The brain weighed 1380 grams, its surface was smooth, its convolutions normal. The ventricular systems appeared normal and the sella turcica was of the usual size. The pituitary gland revealed no gross abnormalities but on section a large metastatic focus of neoplasm was found in the anterior lobe. The cells were irregular in solid cords and clusters and vaguely columnar.

Summary

1. The subject of hypertrophic pulmonary osteoarthropathy is discussed from the standpoint of etiology and pathogenesis. The need for a logical classification is suggested. Several separate entities are implied which heretofore have been grouped as one disease.

2. Reference is made to the literature, particularly to the work of Fried, pointing to an endocrine basis for this osseous syndrome.

3. Fried's views implicate the pituitary gland as the source of the deranged osseous picture. He suggested a hormonal relationship between the lungs and the pituitary gland.

4. A case is presented which revealed metastasis to the pituitary glands, secondary to lung carcinoma.

Conclusions

1. A case of carcinoma of the lung with chronic hypertrophic pulmonary osteoarthropathy is presented in which metastasis to the anterior lobe of the pituitary gland was found.

2. This case suggests that the overstimulation of the anterior lobe of the pituitary gland by the metastatic lesions was responsible for the picture of hypertrophic osteoarthropathy, thus further enhancing the view that the pituitary gland is responsible for the osseous lesions.

3. Further studies are indicated to establish the etiology of this condition and to separate it from apparently non-related conditions such as clubbed fingers, etc.

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HYPERTENSION CAUSED BY UNILATERAL KIDNEY DISEASE (A FOLLOW-UP REPORT) *

By J. SHIRLEY SWEENEY,† M.D., Sc.D., F.A.C.P., and JOHN M. PACE, M.D., F.A.C.S., *Dallas, Texas*

IN the December 1943 edition of this Journal, we reported a case of hypertension caused by unilateral kidney disease.[1]

The patient (M. J. M.) was at that time unmarried, aged 21, and consulted one of us (J. S. S.) on May 3, 1941. She was referred by her family physician because of high blood pressure. Her family history was entirely negative. Her menstrual history, likewise, was perfectly normal. The only illness that she had had during childhood was measles. She stated that she had had some sort of kidney trouble, the nature of which was not clear; however, she remembered having been in bed for several days, but denied that there was any edema or blood in the urine. She had had an occasional attack of tonsillitis. Her tonsils and adenoids had been removed in 1940. She had had an appendectomy for acute appendix at the age of 13.

Her complaint, when she was first seen, was that of headache. She further stated that she had not felt well for the preceding six or seven months, having noticed fatigue and general malaise especially. Her headaches were basal in location, and were present each morning on awakening. In the latter part of 1940, she developed an upper respiratory infection. The physician who attended her took her blood pressure and found it to be 230 mm. Hg systolic and 120 mm. diastolic. From this time until she was first seen by one of us (J. S. S.), she had lost 12 pounds, was quite nervous, and complained of considerable fatigue in addition to her headaches.

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Her physical examination was essentially negative, except for some slight brownish pigmentation about her face, neck and forearms. There was some tortuosity of the retinal vessels and there were a few angiospastic areas noted on ophthalmoscopic examination. The arteries were moderately narrowed and there was some loss of light reflexes. Heart sounds were good, but forceful, with accentuation of the aortic second sound. The pulse rate was 100. Her pelvis was entirely negative, as was the rectal examination. Her extremities were cool, discolored and moist. Her blood pressure at the time of this examination was 224 mm. Hg systolic and 154 mm. diastolic. Laboratory studies included lateral stereoroentgenogram of the skull, blood chemistry, urea clearance, phenolsulfonphthalein kidney function, perirenal air studies, and a scout film of her abdomen. All of these studies were negative except that in the latter film there was noted a rather small kidney on the right side. She was then seen by one of us (J. M. P.) to be studied urologically. A catheterized

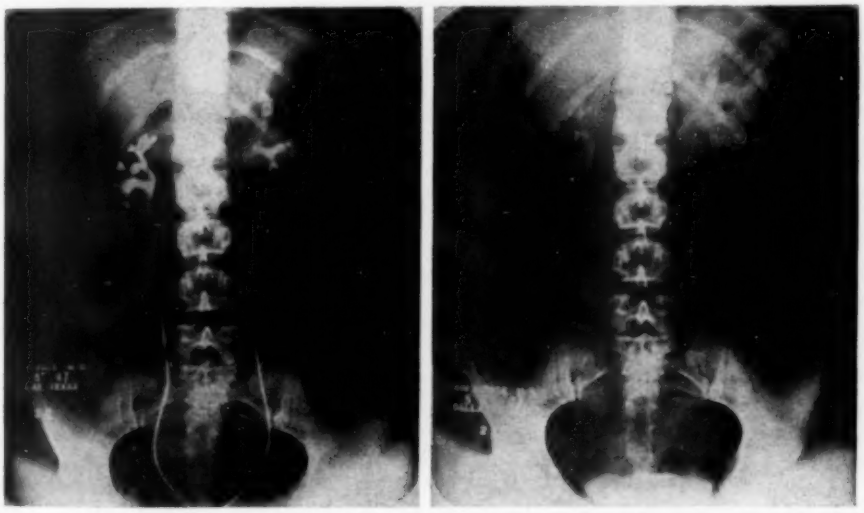

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FIG. 1. Preoperative films May 1941.

(*a*) Right retrograde pyelogram: Small kidney outline with normally appearing pelvis and calices.

(*b*) Excretory urograms: Left—Slight hypertrophy of kidney with normal architecture of the pelvis and calices. Right—Good visualization in a small kidney.

urine was found to contain a small amount of albumin and granular casts. Cystoscopic examination was performed and indigo carmine was returned from the left ureteral orifice in a grade three concentration in 10 minutes, whereas only a faint trace of blue was noted from the right ureteral orifice. A retrograde pyelogram of the right side revealed a small kidney outline approximately one-half the size of the opposite kidney with a normal pelvis and calices. The left retrograde pyelogram was considered quite normal (figure 1a). Cystoscopy was repeated on the following day with the same findings as to the return of the indigo carmine. About 10 days later excretory urograms were made and good visualization was obtained of each kidney in 5, 15, and 25 minute films (figure 1b). About two weeks later the patient was subjected to another cystoscopy. Phenolsulfonphthalein was used intravenously and at the end of 45 minutes' time 22 per cent of the dye was returned from the left kidney and none from the right. This patient was observed for approximately two months,

particular attention being paid to eye grounds and blood pressure. Her systolic pressure ranged from 210 to 240 mm. Hg and the diastolic level varied from 120 to 140 mm. Hg.

About the middle of June 1941, there was noted a bit of fuzziness about the discs. At this time the patient complained also of mild visual disturbance. She was told that the right kidney was functionless and that she had possibly something to gain and nothing to lose by having it removed. She elected to have the operation, and on July 8 a nephrectomy was done on the right side.

The kidney removed was approximately one-third its normal size. When the patient was returned to her room following the operation, her blood pressure was 145 mm. Hg systolic and 85 mm. diastolic. Four hours later it was found to be 132 mm. Hg systolic and 100 mm. diastolic. The following morning her tension was 130 mm. systolic and 78 mm. diastolic. Twelve days later when she was discharged, the reading was 126 mm. systolic and 78 mm. diastolic.

The kidney grossly was considerably smaller than normal. It measured 10 by 4 by 3 cm. and weighed 60.6 grams. The capsule was thickened but stripped readily and underneath there was a smooth shiny surface. On section the cortex and medulla were very well defined. The cortex averaged 4 mm. in thickness. There was no gross scarring in the parenchyma. The kidney pelvis was not enlarged. There were no stones.

Microscopically, sections through different portions of the kidney revealed very extensive focal chronic inflammatory changes immediately beneath the capsule. In these areas was seen marked condensation of renal tissue with patchy scarring and with loss of tubules and glomeruli. A heavy small mononuclear cell infiltration occurred in these areas. Glomeruli in different states of degeneration were noted, whereas in striking contrast in the remainder of the renal parenchyma the glomeruli were essentially normal. The sectioned blood vessels were noticeably thickened, their lumina being reduced as much as one-third in diameter in numerous areas (see photomicrographs in original article). A section through the pelvis of the kidney revealed slight overgrowth of the pelvic mucosa. A few scattered chronic inflammatory cells were noted beneath. The pathologist, Dr. John L. Goforth, rendered the opinion that there was a chronic active progressive subcapsular pyelonephritis of marked degree.

The patient was seen on numerous occasions following her operation. Approximately two months following operation her eye grounds were strikingly different from the preoperative condition. The fuzziness had entirely disappeared about her discs; there was definite return of some light reflex; and the spasm previously noted was absent.

Her blood pressure varied from 110 to 116 mm. Hg systolic with a diastolic of 72 to 78 mm. The patient gained 15 pounds and went back to her work. She was carefully checked in February 1942, at which time her blood urea nitrogen was 10 mg. per 100 c.c. and her urea clearance was 124 per cent of normal. Repeated urine examinations revealed nothing of consequence. Phenolsulfonphthalein excretion was 50 per cent in the first hour and 9 per cent in the second.

This patient presented only one interesting symptom following her operation, which was that of a momentary dizziness on arising from a recumbent position. This dizziness was rather marked a few months following operation but gradually became less severe, and when last seen the patient was entirely free of this annoyance. The explanation we suggest for this interesting symptom is the obvious lack of cardiac and vascular adaptation to the changed levels of blood pressure. She has subsequently been observed for any possible disease in the remaining kidney.

July 8, 1947, will complete six years postoperative observation. During the six years, the patient has married and now has a child three years of age. She went through her pregnancy with no difficulty, giving birth to a 7½ pound baby. Her

maximum blood pressure reading during her gestation and delivery was 122 mm. over 82 mm. Most of the readings varied from 106 to 110 mm. systolic. Her kidney function remained quite normal throughout the period of her pregnancy.

She was seen on January 25, 1947, by one of us (J. M. P.), complaining of some frequency and dysuria of five days' duration. She also stated that three years previously she developed some slight tenderness in the region of the left kidney, which usually manifested itself a few days before each menstrual cycle, only to disappear after the onset of menstruation. She stated that she never noticed it between her menstrual cycles.

Examination on January 25, 1947, revealed that her blood pressure was 120 mm. systolic and 82 mm. diastolic. A catheterized urine was negative except for 1 plus

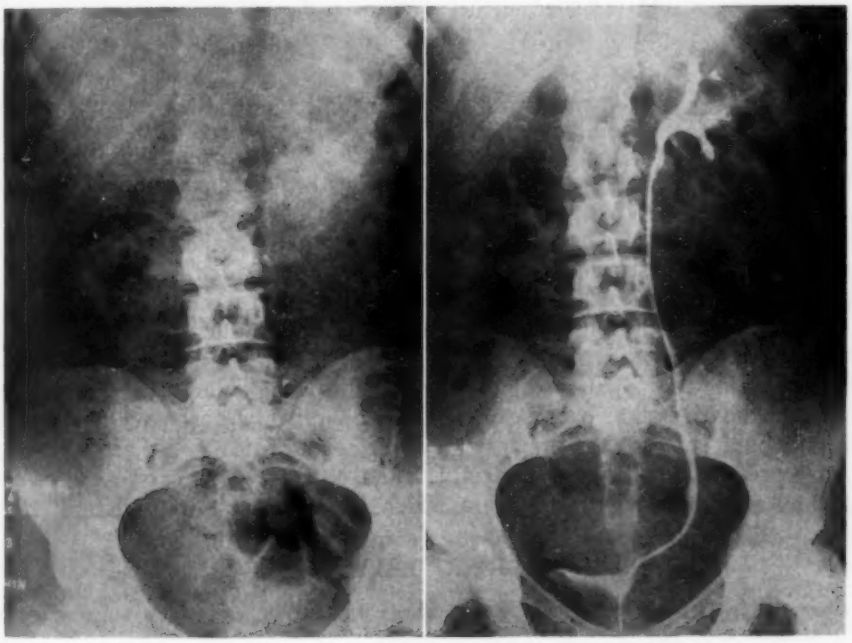

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FIG. 2. February 1947.
(*a*) Excretory urograms. Good function in remaining left kidney.
(*b*) Left retrograde pyelogram. Pelvis and calices presented no abnormalities.

pus with gram negative bacilli. A cystoscopic examination revealed some diminution in the expulsive force of the bladder. A few fine trabeculations were noted on the posterior wall of the bladder. A catheter was passed into the left ureter with no obstruction and a pyelogram was made. There was some slight granulation tissue in the neck of the bladder. The retrograde pyelogram was interpreted as being within normal limits (figure 2b). At this time the patient was placed on ammonium chloride and mandelic acid by mouth. She returned for observation on February 14. On this date she had no bladder symptoms whatsoever, a catheterized urine stain was entirely negative, and a gram stain likewise was negative. Indigo carmine was returned in grade 4 concentration from the left kidney in six minutes. Excretory urograms were made at this time, and a normal function was found in the left kidney,

with some slight dilatation and tortuosity of the upper left ureter (figure 2a). Her blood pressure on February 14, 1947, was 118 mm. Hg systolic and 82 mm. diastolic. She stated that she was feeling exceedingly well and asked whether or not she might become pregnant again. She was advised that, whereas she had come through one pregnancy with no difficulty and has a child of three years, it would be, in our opinion, taking a little bit of risk to add another pregnancy.

SUMMARY

This case has now been followed for seven years. She has had one pregnancy and has a perfectly normal child three years of age, and is maintaining a very normal blood pressure. It was thought of interest to review the findings on this patient, insofar as she had been followed closely and it would seem has been completely cured of her hypertension by removal of a small diseased right kidney.

We are cognizant of the danger inherent in reporting such a case as this, insofar as nephrectomy in hypertension might be too easily assumed to be a cure for hypertension. We feel that all younger individuals, that is, those individuals under the age of 40, who present themselves with a marked elevation of blood pressure, should be thoroughly investigated as to possible kidney disease, especially unilateral. Even when this is found, we further feel that the patient should be most carefully observed for a reasonable period of time before resorting to surgery. This period of observation should convince the clinician that there is no residuum of nor present pathology in the opposite kidney. Finally, it is our conviction that the operation should be placed on more or less of an elective basis, explaining to the patient that surgery might bring about a cure, but, insofar as some of the cases that have been operated upon in the past have not done too well, it is only fair that the patient should be so informed. We are, because of the case presented in this article, convinced that there does exist an occasional individual with marked hypertension which is attributable to unilateral kidney disease.

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RUPTURE OF AMYLOID SPLEEN *

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PRIMARY amyloidosis is an infrequent clinical entity and the search for possible etiological factors presents an interesting theoretical problem. Because of these considerations, as well as the fact that this case presents a unique series of events, an instance of this type of amyloidosis is detailed.

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Case Report

The patient, a 36 year old married white woman, was first seen by one of us (F.K.) because of a mild sore throat and upper respiratory infection. She was obsessed with the possibility of a "streptococcus sore throat" and called a physician for reassurance. Her rectal temperature was found to be 99.2° F. and examination of the throat disclosed only slight redness of the anterior faucial pillar on one side. Moreover, it seemed that most of this inflammation could have been caused by the application of argyrol which the patient had adopted as a therapeutic measure. In the course of further physical examination it was noted that her complexion was sallow. The heart and lungs were found to be relatively normal. The blood pressure was 140 mm. Hg systolic and 90 diastolic. The pulse rate was slightly accelerated. Examination of the abdomen to which, incidentally, the patient objected on the grounds of irrelevance, disclosed the presence of a markedly enlarged liver reaching down to the iliac crest. The liver edge extended from the right iliac crest across the epigastrium at a level of about four or five fingers below the xiphoid and into the left upper quadrant. In the latter area a firm smooth spleen was felt which extended to about four fingers below the left costal margin. There was no lymphadenopathy.

By the disclosure of a hepato-splenomegaly the aspect of the case was entirely altered. Interrogation failed to elicit any relevant complaints. She had not lost weight. There were no gastrointestinal symptoms. There was no history of jaundice or of purpuric manifestations.

The patient's family was informed that it would be advisable to have a hematologic study. Without any prejudgment of the etiology of the hepato-splenomegaly it was felt that this study constituted the first diagnostic approach. It was emphasized that the mild sore throat, in all probability, had no relation to the finding of a hepato-splenomegaly and that all methods of investigation should be exhausted in an attempt to discover the cause. On the following day the patient sought other advice and was told that she had infectious mononucleosis but that leukemia had been excluded. It seemed difficult to accept the diagnosis of mononucleosis as the cause of this syndrome and the patient was urged to have further hematologic study including a bone marrow examination. This was done by Dr. Nathan Rosenthal and revealed a hemoglobin of 89 per cent, with 4,400,000 red blood cells per cu. mm. There was a marked leukocytosis of 22,600 per cu. mm. with a normal differential count. Examination of the bone marrow disclosed no abnormalities. There was no evidence in the blood picture of acute infectious mononucleosis; the heterophile antibody reaction was positive in a dilution of 1:64.

With the exclusion of a blood dyscrasia it became apparent that the investigation of the etiology of the hepato-splenomegaly was only beginning. Arrangements were being made to have the patient come into the hospital for observation when the course of events took a bizarre turn. Five days after the first visit to the patient one of us (F.K.) was excitedly called and informed that the patient had fainted and gone into circulatory collapse. Accordingly she was quickly transferred to the hospital. The history now obtained was that she had had a telephone conversation during which she was very much unnerved, felt faint, fell against a chair and lost consciousness. Following this she complained of weakness, dyspnea, coldness, sweating, thirst and generalized abdominal pain.

On admission the patient was conscious and oriented. Her skin was cold and clammy. There was marked pallor of the conjunctivae and mucous membrane. The tongue was dry. The blood pressure was 52 systolic and 30 diastolic. The pulse was rapid and thready. Examination of the heart and lungs disclosed no abnormalities. The abdomen was slightly distended. There was mild generalized abdominal tenderness with the maximum on the left side. There was some rebound tenderness

and rigidity in the epigastric region. The liver was palpable down to the iliac crest. The spleen was not definitely palpable. The hemoglobin was now only 64 per cent with 3,200,000 red blood cells per cu. mm. The white blood count was 10,600 per cu. mm. with a normal differential. The stool showed a slightly positive guaiac test.

It was felt that the clinical picture was that of shock due to internal hemorrhage. There was, however, no evidence of bleeding into the peritoneal cavity or into a hollow viscus. It was believed that the hemorrhage was most likely retroperitoneal and that a conservative course should be followed.

The patient was given 1,000 c.c. of blood during the night of admission. By the next morning her general condition had improved. The quality of the pulse was better and the blood pressure had risen slightly. The abdomen, however, had become slightly more distended. The liver and spleen could not be palpated. In spite of the transfusions, the hemoglobin had not risen. A surgical consultant at this time interpreted the abdominal distention as evidence of ileus, secondary to retroperitoneal bleeding. On the morning of the third hospital day it was noted that the distention

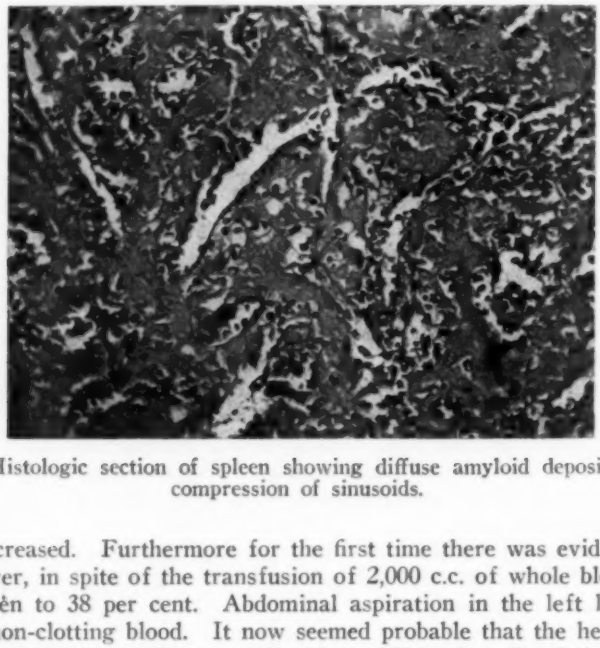

FIG. 1. Histologic section of spleen showing diffuse amyloid deposition with compression of sinusoids.

was further increased. Furthermore for the first time there was evidence of a fluid wave. Moreover, in spite of the transfusion of 2,000 c.c. of whole blood, the hemoglobin had fallen to 38 per cent. Abdominal aspiration in the left lower quadrant yielded frank non-clotting blood. It now seemed probable that the hemo-peritoneum was due to a rupture of the spleen sustained by a fall against the chair. Laparotomy with a view to splenectomy was indicated.

The exploration was performed (G.D.O.) under general anesthesia through a left upper mid rectus muscle splitting incision with a left lateral extension. The abdominal cavity was found to contain about two liters of fresh and clotted blood. It was immediately determined that the source of the bleeding was the spleen. The pedicle of this organ was clamped, hemostasis effected and the spleen quickly removed. The liver was found to be large and unusually smooth. The blood was removed from the peritoneal cavity and the abdomen closed by means of interrupted, buried, figure of eight, steel wire sutures. Penrose drainage to the tail of the pancreas was instituted. The patient continued to receive blood transfusions during and after the operation. She weathered the procedure well and made an uneventful recovery.

The spleen weighed 1,400 grams. It was encased by a large subcapsular hematoma. The capsule at one point showed a small tear. On removal of the hematoma the spleen was found to be of a reddish color and of rubbery consistence. A small tear was found in the splenic parenchyma from which the hemorrhage evidently had originated. A cross section of the spleen disclosed a diffusely homogeneous surface having a distinct waxy appearance and salmon pink color. The Malpighian follicles were entirely obliterated. Histologic section and staining reaction disclosed diffuse and marked amyloidosis (figure 1).

It was now possible to reconstruct the clinical course of events. The original sore throat had of course no relation to the illness which was accidentally discovered. Apparently this patient, having diffuse amyloidosis of the liver and spleen, had a syncopal attack and fell with her left side against a chair causing a small rupture of the spleen. This caused a subcapsular hemorrhage which gave rise to the original symptoms of shock. The subcapsular hematoma increased in size and finally caused a rent in the capsule which allowed for bleeding into the free peritoneal cavity.

We were now intent on appraising the extent of involvement with amyloid as well as investigating the etiology of this metabolic disorder. Moderate involvement with amyloid could be inferred from the Congo red test which showed 64 per cent retention. There was ample evidence of renal involvement in the presence of marked albuminuria as well as occasional granular and hyaline casts. Total blood protein was only slightly reduced to 5.0 gm. per cent, the albumin fraction being 3.2 gm. per cent and the globulin 1.8 gm. per cent. However, the kidney was able to concentrate to a specific gravity of 1.022. The blood urea nitrogen was normal. The urine did not contain amyloid casts or refractile lipoids. The intravenous pyelogram disclosed no abnormalities. There was no evidence of disturbed liver function. The cephalin flocculation test was negative. The blood cholesterol was 400 mg. per cent of which the esters were 300 per cent. There was no clinical jaundice.

An attempt to detect classical etiologic factors yielded no results. There was no history of tuberculosis contact and the roentgenogram of the chest disclosed no abnormalities. There was a vague history of a tooth infection with associated peridental suppuration. However, a roentgen-ray of the mandible disclosed no osteomyelitis or other abnormalities. There was no clinical evidence of lues and the Wassermann reaction was negative. We were consequently in a position to assume that this patient had primary amyloidosis.

One year after operation the patient's general condition is fairly satisfactory. However, she continues to have marked albuminuria and is developing fixed hypertension (170/110), possibly due to amyloid disease of the kidneys with contraction. The liver has not changed in size.

Comment

Several provocative hypothetical considerations regarding the etiology of amyloid degeneration arise from both experimental and clinical experiences and may be pertinent. Kuczynski [1] was the first to produce amyloid in mice by feeding them casein-rich food, as well as by injecting such a casein preparation as nutrose. This has been repeated by others.[2, 3, 4] In conjunction with these experimental observations the clinical experiences in the Orient recorded by Snapper [5] would seem to be significant. Snapper points to the rarity of amyloid disease in the Orient compared to the incidence of this disease in America. Thus out of 2,046 consecutive autopsies on Chinese patients he found five cases of amyloidosis, representing an incidence of 0.25 per cent. This contrasts sharply with the experience at the Philadelphia General Hospital where out of 3,047 con-

secutive autopsies there were 50 cases of amyloidosis and at Montefiore Hospital, New York City, where out of 1,727 consecutive autopsies there were 125 instances of amyloidosis. Moreover, a comparison of incidence of amyloidosis in cases of tuberculosis, which appears to be a prominent factor in its causation, is even more impressive. Thus at the Peiping Union Medical College Hospital Snapper records only three cases of amyloid among 240 tuberculous patients. This contrasts strikingly with the reports of Rosenblatt and also of Fishberg, quoted by Snapper, which record an incidence of about 25 per cent of amyloid degeneration in autopsies on tuberculous patients. Although it is only speculation, a plausible explanation of this difference is given by Snapper which has regard for the experimental experiences mentioned before. It is pointed out that dairy products are absent from the diet of North China while these casein-rich products are partaken of abundantly in the Western world. It may be, therefore, that, especially in the presence of tuberculosis or suppuration, amyloidosis is much more likely to occur in people whose dietary habits include the ingestion of plentiful amounts of casein products.

The aforementioned facts may have some relevance to the above reported case. This patient, for the purpose of improving her health, had adopted the habit of drinking large amounts of milk and a moderate sized portion of cheese each day during the three years preceding the detection of her illness. No other etiologic or predisposing cause for amyloidosis could be discovered.

It has been observed that amyloid deposits have been spontaneously resorbed in mice. A few investigators, notably Waldenström,[6] have reported observations tending to show resorption of deposits in clinical cases of amyloidosis. Since the latter observations are based either on aspiration biopsies or clinical pathological tests they are not entirely conclusive. In the experience of Dr. Klemperer [7] no unequivocal instance of absorption of amyloid has been observed.

From the surgical viewpoint, it may be stated that rupture of an enlarged diseased spleen, as in this instance, is caused by trauma which would be insufficient to cause rupture of a normal viscus. Rupture of an amyloid spleen with hemoperitoneum, successfully treated by splenectomy, must be a rarity. It has not been encountered before at this hospital.

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EDITORIAL

SURGICAL MEASURES FOR THE RELIEF OF INTRACTABLE ANGINAL PAIN

ALTHOUGH the pain of coronary artery disease can usually be controlled by rest and other appropriate conservative measures, there are occasional cases in which this is impossible. Frequently recurring attacks of severe pain, coming on with the slightest exertion or even while at rest, not only are incapacitating and torturing to the victim but may constitute a grave risk to life in themselves. In such cases radical measures which offer a reasonable prospect of relief are fully justified if the operative hazard is not prohibitive and if the untoward results that may follow are not too disturbing. It is natural, therefore, that neurosurgeons have tried various operative measures in such cases.

The surgical procedures which have been employed have been designed with three primary objectives in view: to cut afferent pathways and prevent painful impulses from reaching the nervous system; to cut efferent pathways and interrupt vasoconstrictor impulses which might cause or increase spasm of the coronary vessels; and to provide a source of anastomotic circulation to supplement the inadequate blood flow through the coronaries.

The latter would be the preferable procedure if a practicable and effective method could be devised to accomplish it. The evidence at present strongly favors the view that the immediate cause of anginal pain is ischemia of the myocardium. If a significant increase in blood flow could be achieved, this might not only relieve pain but presumably also improve the nutrition and functional capacity of the myocardium. Beck[1] attempted to accomplish this by exposing the heart widely and suturing flaps of intercostal muscle to the myocardium. O'Shaughnessy[2] utilized omental grafts in a somewhat similar way. Attempts have also been made to create extensive pericardial adhesions by applying irritants to the pericardium. Thus far there is no adequate evidence that any of these measures are effective. It seems questionable indeed whether the blood flow can be notably increased in this way in a myocardium with marked and extensive sclerosis of its vessels, and at best relief would be slow as the development of a collateral circulation is a gradual process. The operative mortality reported following Beck's operation of 37.8 per cent is virtually prohibitive. The possibilities of such measures, however, have by no means been exhausted, and further study is desirable; but their use as therapeutic measures is not yet warranted.

Attempts to interrupt pain pathways stem from Jonnesco's report (1920) of four cases in which anginal pain was relieved by removal of the cervical sympathetic ganglia. This work aroused considerable interest, and during the subsequent decade a large number of similar operations were carried out,

[1] BECK, C. S.: Principles underlying the operative approach to the treatment of myocardial ischemia, Ann. Surg., 1943, cxviii, 788–806.

[2] O'SHAUGHNESSY, L.: Surgical treatment of cardiac ischemia, Lancet, 1937, i, 185–199.

varying somewhat in detail and extensiveness. The results were not satisfactory, since even after bilateral removal of the entire cervical sympathetic chain and stellate ganglia adequate relief was obtained in only a little over half of the cases. This was at the cost of an early postoperative mortality rate of about 20 per cent.

The reason for the relative ineffectiveness of these operations was clear when more precise knowledge was obtained regarding the distribution of the afferent fibers from the heart. The principal group of fibers leave the heart in the superior, middle and inferior cardiac nerves which join the sympathetic chains on both sides in the region of the superior, middle and inferior cervical ganglia respectively. No connections have been demonstrated between these ganglia and the cervical spinal nerve roots. The afferent fibers turn back and pass down the sympathetic chain, then run through the rami communicantes to the posterior roots of the upper thoracic nerves and thence enter the cord. Excision of the stellate ganglion (formed by fusion of the inferior cervical and first thoracic sympathetic ganglia) effectively interrupts these tracts. In addition, however, there are afferent fibers passing directly from the cardiac plexus to the second, third and sometimes the fourth thoracic sympathetic ganglia and entering the cord through the corresponding posterior roots (and possibly also the fifth). These fibers are not interrupted by a complete cervical sympathetic ganglionectomy, and they provide ample means for conveying painful impulses in these cases.

These relationships are well shown by such experiments as those of White et al.[3] in dogs, who demonstrated that pain caused by temporary constriction of the descending branch of the left coronary artery could be abolished either by excision bilaterally of the stellate ganglia and the upper four thoracic sympathetic ganglia, or by section of the upper five thoracic posterior roots. The distribution in man seems to be quite similar to that in the dog.

Reasonably effective measures for the relief of pain date from the work of Mandle (1925) and Swetlow (1926) who reported that anginal pain was relieved by infiltration of the upper four pairs of thoracic sympathetic ganglia with alcohol. White[4] further perfected the technic of these injections, and he has recently[5] summarized the results obtained in 75 patients. In this series, good results with virtually complete relief of pain on the side or sides injected were obtained in 56 per cent and fair results with substantial reduction in severity of the pain in 21 per cent. No appreciable relief was obtained in 8 per cent, and 8 per cent died as a result of the procedure. Many of the patients were gravely ill, and the risk of an operation any more extensive would have been prohibitive.

The chief advantages of procaine-alcohol injection are that a general

[3] WHITE, J. C., GARREY, W. E., and ATKINS, J. A.: Cardiac innervation: Experimental and clinical studies, Arch. Surg., 1933, xxvi, 765–786.

[4] WHITE, J. C.: Technique of paravertebral alcohol injection: Methods and safeguards in its use in the treatment of angina pectoris, Surg., Gynec. and Obst., 1940, lxxi, 334–343.

[5] WHITE, J. C.: The surgical relief of severe angina pectoris, Medicine, 1948, xxvii, 1–42.

anesthetic is not required; and that if skillfully done it involves relatively little discomfort or disturbance to the patient, so that it can be carried out on patients too gravely ill to withstand an open operation. It does require a high degree of specialized skill and constant practice, and even with this about 10 per cent are failures. Serious results may follow accidental injection into the pleura or particularly the subdural space. In many of the cases there developed an intercostal neuralgia from chemical injury of the intercostal nerves which was severe in 10 per cent. This usually cleared up after a few months, but occasionally it was persistent, continuous and very distressing, and rarely it required section of the posterior nerve roots for relief.

The results are not always permanent. In 40 of White's cases there was no recurrence of pain during the period of observation (up to nine years), but pain did recur after two and one-half months to five years in 14 others. Relief from a second injection is likely to be briefer and less satisfactory. If the pain is bilateral or if it appears later in severe form on the opposite side, injections on the second side are required.

In patients who can withstand an open operation under general anesthesia, the same results can be obtained with more precision and certainty by excision of the stellate ganglion and the upper four (possibly three only) thoracic sympathetic ganglia. In this way injury to the intercostal nerves can largely be avoided as well as the occasional accidents resulting from misplacement of the needle. A second operation is required if the pain is bilateral. This operation has been used, among others, by White who has reported eight cases with one death from secondary infection.[5] Relief was satisfactory in all cases in which all three thoracic ganglia were removed, but there was recurrence of some pain in two, attributed to a regeneration of nerve fibers.

Lindgren and Olivecrona[6] have reported a series of 71 patients in whom this operation was carried out. Relief was essentially complete in 44 per cent and substantial in 41 per cent. Results were unsatisfactory in 7 per cent, and six deaths occurred within one month, three as an immediate result of the operation. No precise data are given as to the duration of the relief. In 17 of the 29 cases obtaining only partial relief, however, "migration" of pain occurred to areas previously uninvolved or in which only minor discomfort had been felt. This was usually to the opposite side of the chest, and it could be relieved by a second sympathetic ganglionectomy on that side.

In a few cases observed both by White and Olivecrona, however, the pain was felt in the neck and jaw. This was not relieved by any of the usual operative procedures. That these pains are truly anginal is shown by their appearance following exertion and by their relief by nitroglycerine. The pathways transmitting this pain are not known. It has been suggested that they may pass through possible undiscovered connections between the upper

[6] LINDGREN, I., and OLIVECRONA, H.: Surgical treatment of angina pectoris, Jr. Neurosurg., 1947, iv, 19–39.

cervical sympathetic trunk and the cervical posterior nerve roots or (more probably) through the vagi. In one severe case, Olivecrona obtained relief by a bilateral tractotomy which produced analgesia in the distribution of the mandibular branches of both trigeminal nerves.

The most troublesome sequela was pain in the the arm lasting for one to two months, which Olivecrona attributed to a "traumatic neuritis." This was usually mild, but in some cases it was severe, in one case requiring section of the posterior nerve roots for relief.

Section of the upper four (possibly five) thoracic posterior nerve roots will also interrupt the afferent pathways from the heart. This was shown, e.g., by the animal experiments of White et al.[3] The operation, which requires an extensive laminectomy under general anesthesia, was regarded by them as too dangerous for such poor surgical risks. Other surgeons, however, have employed it with apparent success, notably Ray.[7] The great advantage is that a bilateral exposure is obtained, and the roots on both sides can be cut at a single operation.

White [5] collected from the literature reports of 30 cases with a mortality of 10 per cent. "Complete relief" was reported in all but one case. Olivecrona,[6] on the other hand, reported that the results in seven cases (with one death) were much less satisfactory than those obtained by sympathetic ganglionectomy. Some troublesome sequelae were observed, including anesthesia dolorosa in one case.

The theoretical objection that has been raised to all of these operations that they would endanger the patient by eliminating his warning signal on dangerous overexertion has not been substantiated. All observers agree that such a signal is regularly retained, either as a sense of constriction, dyspnea or dull pain which may be severe if it is referred to the neck or jaw.

Another advantage of the operations is that the sense of apprehension during an attack is usually reduced or eliminated, even if pain is not adequately relieved. In most instances, also, patients who later had fatal attacks of coronary occlusion suffered little or no pain on the side or sides which had been denervated.

Little reference has been made thus far to the part that section of the efferent (vasopressor or vasoconstrictor) fibers may play in the relief obtained by these operations, and there is great difference of opinion regarding this point. As no such efferent fibers are known to pass through the posterior roots, the relief following posterior rhizotomy presumably is due solely to eliminating the afferent pathways. Relatively little is known as to the course of the efferent fibers. There is not even agreement as to whether they come through the vagus or the sympathetics. There is at least a strong presumption, however, that some efferent pathways are interrupted by the sympathetic ganglionectomies. It has been suggested that this is the explanation for the relief obtained by a substantial minority of the patients following restricted ganglionectomies in which some afferent pathways were

[7] RAY, B. S.: The management of intractable pain by posterior rhizotomy, Proc. Assoc. Res. Nerv. and Mental Dis., 1943, xxiii, 391–407.

not disturbed. In cases with advanced sclerosis and generally rigid arteries vasoconstriction seems relatively unimportant, but it may well be significant in those patients whose arteries still possess some resilience.

Fauteux,[8] on the basis of experiments with dogs, has advocated a different procedure designed to interrupt both pathways and improve the coronary circulation. This consists of a ligation of the great cardiac vein, a pericoronary artery neurectomy or both. He reported 16 cases, in most of which only a venous ligation was done, with three deaths. Relief of pain is said to have been obtained in most, and some patients were able to resume their former occupations. It is impossible at present to assess either the value or the risk of this procedure which is still distinctly experimental.

In summary, patients with even severe coronary disease withstand anesthesia and operations of this magnitude far better than might be anticipated, provided the myocardium has not suffered excessive injury from a recent infarct. At present operation is not warranted in patients whose attacks can be controlled reasonably well by conservative measures. If a competent neurosurgeon is available, patients with severe intractable angina, provided their condition is not excessively bad, can be promised an excellent prospect of substantial if not complete relief of pain by a suitable operative procedure. For patients in precarious condition paravertebral injections of procaine followed by alcohol without general anesthesia is the least hazardous, it may justifiably be tried in desperately ill patients if the need is very urgent, and it usually gives satisfactory results. With patients in better condition, open operation offers a somewhat better prospect of obtaining satisfactory relief, with less risk of untoward results. Neither ganglionectomy nor posterior rhizotomy has at yet been shown to be clearly superior to the other, although the evidence now seems slightly to favor ganglionectomy. For patients with bilateral pain, however, rhizotomy offers the big advantage that the roots can be cut bilaterally at a single operation whereas ganglionectomy is a two stage operation with an interval of at least one or two months between.

A substantial price is exacted for this relief. There is an early postoperative mortality in all these procedures of about 10 per cent, varying with the care used in selecting patients and with where the line is drawn between presumably operable and inoperable cases. In most cases temporary discomfort or pain of various types and severity follows, and occasionally this is severe and persistent.

These procedures are only palliative. There is little evidence that the function of the myocardium is significantly improved or the average duration of life materially prolonged, although this seems to have been accomplished in certain individual cases. Even this price does not seem excessive for properly selected patients with severe intractable pain, and the preliminary work with these operations seems to have reached a point which warrants their more extensive use. P. W. C.

[8] Fauteux, M.: Surgical treatment of angina pectoris. Experiences with ligation of the great cardiac vein and pericoronary neurectomy, Ann. Surg., 1946, cxxiv, 1041–1046.

REVIEWS

Textbook of Endocrinology. By HANS SELYE, M.D., Ph.D. (Prague). 914 pages; 18 × 26 cm. Acta Endocrinologica, Université de Montreal, Montreal, Canada. 1947. Price $12.80.

In this book Selye brings together a vast amount of endocrinological data scattered through the fields of anatomy, physiology, pathology and medicine and in so doing argues for the establishment of endocrinology as a separate discipline. It is perhaps premature to justify such an attempt on pedagogical grounds, but there is no questioning its desirability as a matter of principle. As now taught in most medical schools endocrinology is presented in a series of fragments and it is left to the student to put the pieces together. How well he succeeds is a matter of opinion. It is to Selye's credit that he circumvents in one field at least the unfortunate consequences of departmentalized teaching.

The book itself is a mine of information and will well repay the time and effort of anyone interested in endocrinological matters, whether it be from the clinical or experimental point of view. The text itself is concise and always to the point and the arguments are ably presented and easy to follow. The book is perhaps too heavily weighted on the clinical side, but this is not a serious defect and the multitudinous charts, diagrams, tables and illustrations more than compensate for it. In the matter of illustrations alone the work deserves the highest praise. It is hard to see how they could be improved. The author has brought together a very impressive array of clinical photographs, practically all new, unequalled elsewhere. They will serve as a source of illustrative material for texts in all medical fields for years to come. The diagrams, too, are excellent and emphasize the trend, so apparent in the biological as well as the physical sciences, of presenting information in a graphic form. Such presentations stimulate conceptual thinking for they depend more on the use of signs and symbols than upon the written word. The reader is thus encouraged to think dynamically.

In a book which purports, according to its title, to cover the entire field of endocrinology it is unfortunate that there is such a paucity of material concerning the endocrines in plants and invertebrates, and even in the lower vertebrates. No doubt there is little here to interest the clinician, but this does not justify their dismissal in quite so casual a fashion from a text which claims to be all inclusive. Perhaps it might better have been called a textbook of mammalian endocrinology.

Certain parts of the book are highly speculative and represent the author's own views. The reader must be on his guard not to confuse fact with interpretation. The advanced student no doubt can make this distinction easily enough, but the beginner might well be led astray. The author is aware of this difficulty and warns the reader in the preface, but it is questionable whether such warnings really serve their purpose.

The absence of any detailed bibliography is explained as a matter of deliberate policy and no exception can be taken to the author's position on this point. A list of monographs and pertinent papers is found at the end of each chapter and will serve adequately to orient anyone who wishes to familiarize himself with the literature on the subject. The index is one of the book's best features and the author cannot be commended too highly for the splendid job he has done. It adds greatly to the value of the book, which is truly encyclopedic in scope, and immeasurably enhances its value to the student and the investigator. No serious student of endocrinology can afford to do without this work.

D. C. S.

Dermatologic Clues to Internal Disease. By HOWARD T. BEHRMAN, M.D., Assistant Clinical Professor of Dermatology, New York University College of Medicine. 165 pages; 16 × 23.5 cm. Grune and Stratton, Inc., New York. 1947. Price, $5.00.

This book represents an interesting and new approach to the problem of cutaneous medicine. The author attempts to point out that the skin serves as a mirror to reflect evidences of the pathologic processes which may be going on in the body.

He has arranged the various diseases in alphabetical order, using in each case the simplest possible nomenclature. Each paragraph is concise and to the point. There is complete absence of any redundant material. The author has adequately illustrated his text but, unfortunately in some respects, it is apparent that the photographs have been poorly reproduced on the printed page as some of them appear too dark.

The subject matter of this text is excellent but it is to be hoped that the author may see his way clear to enlarge it and write a more complete description of each disease.

H. M. R.

An Introduction to Physical Methods of Treatment in Psychiatry. 2nd Ed. By WILLIAM SARGANT, M.R.C.P., D.P.M., and ELIOT SLATER, F.R.C.P., D.P.M. 215 pages; 14 × 22 cm. The Williams & Wilkins Company, Baltimore, Maryland. 1948. Price, $3.50.

The authors are leading exponents in the application of surgical and medical technics to psychiatric problems. The methods proposed have increased in vogue partly because of demonstrated effectiveness, partly because physicians are oriented organically rather than psychologically.

The book is not intended and should not be considered an introductory text to psychiatric practice. More conservative methods have equal and frequently more sustained effect. Skill in psychotherapy remains the most essential therapeutic technic although its limited availability has encouraged recourse to physical methods. The obvious objection to physical methods, that diseases with demonstrable psychogenic etiology are to be treated organically, is countered by the authors through assumption of "inborn determinants" and organopathy which will eventually be demonstrated. Their methods have, according to the authors, "proved their worth without any theoretical justification."

Disputants will complain that the proponents of physical methods have revived unsupported speculations on inevitable and resistant constitutional factors, and that their technics are variations of organic assaults which have always been known to alter or sometimes induce personality disorder. Most psychiatrists still consider some of these methods, such as leucotomy, as experimental and even desperate. Most concede shock therapy is effective in treatment of the so-called "suicidal psychoses." Few psychotherapists place much stock in the use of drugs as anything but temporary palliatives that add to the array of tokens on which the patient becomes dependent.

The authors state emphatically that physical methods of treatment are being neglected by psychiatrists. Few psychiatrists do not accept the eclectic viewpoint of the authors, that all possible avenues of therapy are to be considered. Most would not agree that physical methods of treatment are being overlooked. The usual findings are that radical methods are abruptly applied without thorough study of the patient's problems and observations as to the effect of conservative management.

Although not personally sympathetic to some of the suggested technics or in agreement as to what can be expected from them, this reviewer knows of no other

text which attempts to justify with equal persuasion, literary style and clarity, the somatic approach to mental illness. The book inspires regret that psychopathology and psychotherapy cannot be imparted as briefly or graphically.

P. S. W.

Procedure in Examination of the Lungs. By ARTHUR F. KRAETZER, M.D.; revised and with a preface by JACOB SEGAL, M.D., F.A.C.P., F.C.C.P. 150 pages; 14 × 21 cm. Oxford University Press, New York. 1947. Price, $3.50.

The present text is the third edition of this work on the fundamentals of the elements of physical diagnosis. The author in his introduction, emphasizes the importance of the induction method of learning physical diagnosis and points particularly to its value in the early diagnosis of tuberculosis. The years since the first edition of this book was written have witnessed the ascendancy of the roentgen-ray in the early diagnosis of pulmonary tuberculosis and have lessened the importance of emphasis on physical diagnosis. But the emphasis in this text is truly not on the early diagnosis of tuberculosis but on the acquiring of the art of physical diagnosis as it applies to all pulmonary diseases. This book then is unique in its value to students to guide them through the methods of developing skill in learning physical diagnosis and how to translate these findings into the diagnosis and the differential diagnosis of chest diseases.

The author employs a simple and logical method in furthering his purpose. The elements of physical diagnosis are set down: inspection, palpation, percussion, and auscultation. These elements are described as they exist in the normal chest. Then the variations from normal in fundamental pathological conditions are described. The student is encouraged always to think not of specific disease conditions but rather to gather facts found under the elements of physical diagnosis and work these facts into a diagnosis. This method is the induction method of learning and utilizes one's skill and not merely memory.

The author has a special interest in pulmonary tuberculosis and has included a chapter on the signs and diagnosis of pulmonary tuberculosis. The teaching of students is certainly deficient in the thorough understanding of tuberculosis but in the broader sense this deficiency applies to all chest disease, since physical diagnosis is the skill which is so often poorly acquired because of improper teaching methods.

An appendix has been added to include the important rôle of bronchial disease particularly in pulmonary tuberculosis. Bronchoscopy and bronchography are briefly mentioned. The growing importance of the roentgenogram is mentioned but the author reiterates his faith in the elements of physical diagnosis.

This book is certainly of value to students who are being introduced to the art of physical diagnosis. The practicing physician will upon reading this book find a fresh interest in this important subject.

M. W. J.

BOOKS RECEIVED

Books received during June are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Arterial Hypertension. By DAVID AYMAN, M.D., Instructor in Medicine, Tufts College Medical School, etc. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (Am. Med. Assoc.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard Uni-

versity, etc. Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work; 24 × 16 cm. 1948. Oxford University Press, New York. Price, $2.50.

Bright's Disease. By HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (Am. Med. Assoc.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work; 24 × 16 cm. 1948. Oxford University Press, New York. Price, $9.00.

Clinical Laboratory Methods and Diagnosis: A Textbook on Laboratory Procedures with Their Interpretation—4th ed. (In Three Volumes.) By R. B. H. GRADWOHL, M.D., D.Sc., F.R.S.T.M. & H. (London), Director of the Gradwohl Laboratories and Gradwohl School of Laboratory Technique, etc. Co-author (on Volume III): DR. PEDRO KOURÍ, Director, Institute of Tropical Medicine, etc. Three-volume set contains approximately 3300 pages; 26 × 18 cm. 1948. The C. V. Mosby Company, Saint Louis 3. Price, $40.00 for three-volume set.

Corazon Pulmonar E Insuficiencia Coronaria. By DR. JUAN GOVEA, de la Facultad de Medicina de Paris, etc. 178 pages; 25 × 16 cm. 1948. M. V. Fresneda (Editor), Havana, Cuba. Price, $4.00.

The Engaged Couple Has a Right to Know (A Modern Guide to Happy Marriage). By ABNER I. WEISMAN, M.D., Assistant Visiting Gynecologist and Obstetrician, Metropolitan Hospital, etc. Foreword by DR. ABRAHAM STONE. 256 pages; 21.5 × 14.5 cm. 1948. Renbayle House, New York. Price, $3.00.

A History of the Heart and the Circulation. By FREDERICK A. WILLIUS, M.D., M.S. in Med., Senior Consultant in Cardiology, Mayo Clinic, etc., and THOMAS J. DRY, M.A., M.B., Ch.B., M.S. in Med., Consultant, Section on Cardiology, Mayo Clinic, etc. 456 pages; 24 × 15.5 cm. 1948. W. B. Saunders Company, Philadelphia. Price, $8.00.

Klinisch-Praktische Bewertung des Elektrokardiogramm-befundes. Volume I. By PRIVATDOZENT DR. OSKAR V. ZIMMERMANN-MEINZINGEN. 227 pages; 23.5 × 15.5 cm. 1948. Verlag Wilhelm Maudrich, Wien, Germany. Price, $8.00.

Practical Bacteriology, Hematology, and Parasitology—10th ed. By E. R. STITT, M.D., Ph.M., Sc.D., LL.D., Rear Admiral, Medical Corps, etc.; PAUL W. CLOUGH, M.D., Physician-in-Charge of the Diagnostic Clinic, Johns Hopkins Hospital, etc., and SARA E. BRANHAM, M.D., Ph.D., Sc.D., Senior Bacteriologist, National Institute of Health, etc. 991 pages; 23.5 × 16 cm. 1948. The Blakiston Company, Philadelphia 5. Price, $10.00.

Subacute Bacterial Endocarditis—2nd ed. By EMANUEL LIBMAN, M.D., Late Consulting Physician, The Mount Sinai Hospital, New York City, and CHARLES K. FRIEDBERG, M.D., Adjunct Physician, The Mount Sinai Hospital, New York City. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (Am. Med. Assoc.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc. Reprinted from Oxford Loose-Leaf Medicine with the same page numbers as in that work; 24 × 16 cm. 1948. Oxford University Press, New York. Price, $3.50.

Symposium on the Use of Isotopes in Biology and Medicine. Contributors: HANS T. CLARKE, HAROLD C. UREY, GLENN T. SEABORG, PAUL C. AEBERSOLD, ALFRED O. NIER, CHARLES D. CORYELL, MARTIN D. KAMEN, DONALD B. MELVILLE,

DAVID B. SPRINSON, HARLAND G. WOOD, KONRAD BLOCK, DAVID M. GREENBERG, I. L. CHAIKOFF, JOSEPH G. HAMILTON, BYRON E. HALL, SAUL HERTZ, WILLIAM F. BALE, JAMES J. NICKSON, and FARRINGTON DANIELS. 445 pages; 24 × 16 cm. 1948. The University of Wisconsin Press, Madison. Price, $5.00.

Thyroid Enlargement and Other Changes Related to the Mineral Content of Drinking Water (With a Note on Goitre Prophylaxis)—Medical Research Council Memorandum No. 18. By MARGARET M. MURRAY, J. A. RYLE, BEATRICE W. SIMPSON and DAGMAR C. WILSON. 39 pages; 24 × 15.5 cm. (paper-bound). 1948. H. M. Stationery Office, London. Price, Ninepence, net.

The Training of a Doctor. REPORT OF THE MEDICAL CURRICULUM COMMITTEE OF THE BRITISH MEDICAL ASSOCIATION. 151 pages; 24.5 × 15.5 cm. (stiff cardboard binding). 1948. Messrs. Butterworth & Co., Ltd., London. Price, 7s 6d., postage 9d, extra.

Vascular Diseases in Clinical Practice. By IRVING SHERWOOD WRIGHT, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College, etc. 514 pages; 21 × 14.5 cm. 1948. Year Book Publishers, Inc., Chicago. Price, $7.50.

Vitamine und Vitamintherapie. By PROF. DR. MED. EMIL ABDERHALDEN, and PROF. DR. MED. GEORGES MOURIQUAND. 408 pages; 23 × 15.5 cm. (stiff paper binding). 1948. Buchhandlung und Verlag, Hans Huber, Bern. Price, 28 francs.

PHONOGRAPH RECORDS

Stethoscopic Heart Records (Revised), Set M-735 (8 sides). By GEORGE D. GECKELER, M.D. 1948. Columbia Masterworks, Columbia Records, Inc., Bridgeport, Connecticut. Price, $8.00.

COLLEGE NEWS NOTES

Research Fellowships—The American College of Physicians

The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1949–June 30, 1950. The Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. They are for the benefit of physicians who are in the early stages of their preparation for a teaching and investigative career in Internal Medicine. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $2,200 to $3,200.

Application forms will be supplied on request to The American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1948. Announcement of the awards will be made as promptly as is possible.

Medical Specialty Board Notices

American Board of Dermatology and Syphilology, Inc., 60 E. 66th St., New York 21, N. Y.; George M. Lewis, M.D., Secretary-Treasurer. Oral examinations will be held in Ann Arbor, Mich., October 21–23, 1948; written examinations for Group "B" candidates will be held on September 9, 1948. Closing date for applications for these examinations was August 2, 1948.

American Board of Internal Medicine, 1 W. Main St., Madison 1, Wis.; William A. Werrell, M.D., Ass't Secretary-Treasurer. Beginning with 1949, only one written examination will be given each year. The date for the examination will be the third Monday in October of each year, and applications for admission to the examination must be filed by May 1 of that year. The requirement of an interval of a year before re-examination has been waived for candidates who failed the written examination in March, 1948, and they may take another examination in October, 1948.

The American Board of Internal Medicine customarily arranges to give the Part I (written) examination under a local proctor in both Puerto Rico and Hawaii. However, the oral examination (Part II) must be given by members of the Board, or by former members on authority from the present Board. This makes it necessary for candidates from Puerto Rico and Hawaii to come to the States for the Part II (oral) examinations.

The American Board of Pathology, Washington University School of Medicine, St. Louis 10, Mo.; Robert A. Moore, M.D., Secretary-Treasurer. Candidates for examination in pathologic anatomy will come before the examiners on October 8, 1948, and those for clinical pathology, on October 9, 1948, at the University of Chicago, Department of Pathology.

The American Board of Pediatrics, Inc., 718 Royal Union Bldg., Des Moines, Lee F. Hill, M.D., Secretary-Treasurer. Oral examinations will take place at Seattle, Wash., September 10–12, 1948, and at Atlantic City, N. J., November 17–19, 1948.

American Board of Psychiatry and Neurology, Inc., 102 2nd Ave., S.W., Rochester, Minn.; F. J. Braceland, M.D., F.A.C.P., Secretary-Treasurer. Examinations in neurology, psychiatry, and neuropsychiatry will be given at the Langley

Porter Clinic, University of California Medical School, San Francisco, on October 11 and 12, 1948, and at the New York State Psychiatric and Neurological Institutes, New York City, on December 13, 14 and 15, 1948. Applications must reach the Secretary-Treasurer at least 90 days before the examination date.

AMERICAN BOARD OF RADIOLOGY, 102 2nd Ave., S.W., Rochester, Minn.; B. R. Kirklin, M.D., F.A.C.P., Secretary-Treasurer. Examinations will be conducted at Tampa, Fla., November 1–5, 1948, and at Atlantic City, N. J., May 31–June 4, 1949.

THE ROYAL COLLEGE OF PHYSICIANS AND SURGEONS OF CANADA, 150 Metcalfe St., Ottawa, Ont., Can.; John E. Plunkett, M.D., F.R.C.P.(C), F.A.C.P., Honorary Secretary. Written examinations will be held in Vancouver, Edmonton, Saskatoon, Winnipeg, London, Toronto, Kingston, Montreal, Quebec City and Halifax: for Fellowship, on October 25, 26 and 27, 1948; for certification, on October 25 and 26, 1948. Oral and clinical examinations will be given at Montreal: for certification, on November 8 and 9, 1948; for Fellowship, November 15 to 23, 1948. Closing date for applications for these examinations was June 25, 1948.

POSTGRADUATE COURSES OFFERED BY OTHER INSTITUTIONS

PSYCHIATRY AND NEUROLOGY, August 30–November 19, 1948, Langley Porter Clinic, University of California Medical Center, San Francisco 22, Calif. Dr. Karl M. Bowman, Professor of Psychiatry, will direct. Fulltime course, covering general and child psychiatry, psychobiology, psychoanalysis, psychology and psychopathology, functional and organic psychoses, psychoneuroses, therapy, psychosomatic problems, neuroanatomy, clinical neurology, neuropathology, neurophysiology, electroencephalography, and x-ray diagnosis. Fee, $200.00. Application should be made to Stacy R. Mettier, M.D., Head of Postgraduate Instruction, Medical Extension, at above address.

HEMATOLOGY AND NEUROLOGY, September 13–18, 1948, Chicago Medical Society, 30 N. Michigan Ave., Chicago 2, Ill. Classes at Thorne Hall, Northwestern University. Also CARDIOVASCULAR AND RESPIRATORY DISEASES, September 20–25, 1948. Detailed course rosters available. Fee, $50.00 each course. Application should be made to W. O. Thompson, M.D., Chairman, Committee on Postgraduate Medical Education, above address.

MISSISSIPPI REGIONAL MEETING

A meeting of Mississippi members of the College took place in Jackson, Miss., at the Heidelberg Hotel on July 25, under the leadership of Dr. John G. Archer, F.A.C.P., College Governor for the State. The meeting began with a luncheon for members and their guests. A scientific session followed, at which papers were presented by L. T. Carl, M.D., F.A.C.P., Jackson, on "Malignant Hypertension"; by Lucian M. Ferris, M.D. (Associate), and G. H. Martin (by invitation), Vicksburg, on "The Treatment of Herpes Zoster by Autonomic Nerve Block"; and by Edgar Hull, M.D., F.A.C.P., New Orleans, College Governor for Louisiana, on "Recent Advances in the Treatment of Heart Disease."

DR. IRONS TO BE NEXT PRESIDENT OF THE AMERICAN MEDICAL ASSOCIATION

At the recent 97th Annual Session of the American Medical Association, Dr. Ernest E. Irons, F.A.C.P., of Chicago, was elected to the post of President-Elect for 1948–1949. He will succeed in 1949–1950 the newly installed President of the

Association, Roscoe L. Sensenich, M.D., F.A.C.P., of South Bend, Ind., who, in turn, succeeded Edward L. Bortz, M.D., F.A.C.P., in that position. Dr. Irons and Dr. Sensenich have both been active for many years in the work of the American Medical Association.

A Regent of the American College of Physicians and its President in 1945–1946, Dr. Irons is Professor of Medicine in the University of Illinois College of Medicine and attending Physician to the Presbyterian Hospital.

On the occasion of retiring as Executive Officer of the Department of Medicine of the College of Physicians and Surgeons of Columbia University, and Director of the Medical Service of The Presbyterian Hospital, Dr. Walter W. Palmer (President of the American College of Physicians, 1948–1949) has prepared an interesting report and record of the activities of the Department and Medical Service during the 26 years, 1921–1947, of his association with those institutions. It is entitled "The Department of Medicine, The Columbia-Presbyterian Medical Center, 1921–1947," and is a history of the Department and its staff during the period.

Grateful acknowledgment is made to Harry R. Litchfield, M.D., F.A.C.P., Brooklyn, N. Y., for his contribution to the College Library of Publications by Members of a copy of "Pediatric Progress, Therapeutics of Infancy and Childhood." Published this year by F. A. Davis Company, Philadelphia, this book is edited by Dr. Litchfield and by Leon H. Dembo, M.D., of Cleveland, Ohio.

The American College of Physicians takes pleasure in reporting that Philip Reichert, M.D., F.A.C.P., New York, N. Y., has become a Life Member by recent subscription.

Dr. Roy R. Snowden, F.A.C.P., was promoted in June from Associate Professor to Clinical Professor of Medicine in the University of Pittsburgh School of Medicine. College Governor for Western Pennsylvania, Dr. Snowden has successfully directed a number of A.C.P. Postgraduate Courses in Internal Medicine, and will this fall direct Course No. 3 which will be offered in Pittsburgh, September 20–October 2, 1948.

A. Carlton Ernstene, M.D., F.A.C.P., has recently been appointed as head of the Division of Medicine in the Cleveland Clinic. A graduate of the College of Medicine of the State University of Iowa, and a former member of the faculty of Harvard Medical School, Dr. Ernstene joined the Clinic staff in 1932 and has served as head of the Section on Cardiovascular Disease for many years.

William B. Castle, M.D., F.A.C.P., Professor of Medicine in the Harvard Medical School, and Associate Director of the Thorndike Memorial Laboratory of the Boston City Hospital, was recently appointed to succeed George R. Minot, M.D., F.A.C.P., as Director of the Laboratory. Dr. Minot has now retired also as Professor of Medicine at Harvard. He had conducted outstanding research in the two institutions for over 30 years, and was awarded a Nobel Prize in Medicine and Physiology in 1934.

Dr. Castle's distinguished investigative work has earned for him honorary degrees from Yale University and the University of Utrecht, the William Proctor, Jr., International Award for Distinguished Service in Promoting Health, the Walter Reed Medal of the American Society of Tropical Medicine, and The John Phillips Memorial Award of the American College of Physicians (1933).

At the recent meeting of the III Interamerican Cardiological Congress, Louis N. Katz, M.D., F.A.C.P., Chicago, Ill., was named Permanent Honorary President of the Interamerican Society of Cardiology.

Dr. Robert Clinton Page, F.A.C.P., has recently accepted appointment as Medical Director of the Arabian American Oil Company, his office being at 711 5th Ave., New York 22, N. Y. The Medical Department of the firm is responsible for an extensive program of care for approximately 25,000 employes in Saudi Arabia, where they have seven hospitals and 22 physicians. Harold H. Golz, M.D., F.A.C.P., also is a member of the Medical Department.

Adolph L. Sahs, M.D., F.A.C.P., has recently been promoted from Acting Head to Head of the Department of Neurology of the University of Iowa College of Medicine.

An honorary LL.D. degree was conferred on Thomas Sim Lee, M.D., F.A.C.P., Washington, D. C., by Mount St. Mary's College, Maryland, on June 2, 1948, in recognition "of his eminent services to Church and State and Citizenry." The citation refers to Dr. Lee's 40 years of service as a physician, to his success as a scholar and teacher at Georgetown and George Washington Universities, his inspiring public lectures, his founding of the Washington Heart Association, and to his many charitable actions. The degree was conferred on the 58th anniversary of the conferral of a similar degree by Mount St. Mary's on Dr. Lee's father, Charles Carroll Lee, M.D.

Philip K. Arzt (Associate), St. Paul, Minn., Assistant Clinical Professor of Neuropsychiatry in the University of Minnesota Medical School, has recently been appointed Senior Consultant in Electroencephalography to that School.

Joseph D. McCarthy, M.D., F.A.C.P., College Governor for Nebraska, was elected to the position of President-Elect of the Nebraska State Medical Association on May 6, 1948.

William C. Menninger, M.D., F.A.C.P., Topeka, Kans., President of the American Psychiatric Association, has been awarded the Chevalier of the French Legion of Honor.

W. Edward Chamberlain, M.D., F.A.C.P., Philadelphia, Pa., has joined a medical mission to Poland and Finland, sponsored by World Health Organization. The purpose of the mission is to bring to the Polish and Finnish people the latest advances in medical, surgical and radiological technics.

University of Colorado Initiates Gold-Headed Cane Ceremony

Some years ago, William J. Kerr, M.D., F.A.C.P., Professor of Medicine and Chairman of the Division of Medicine of the University of California, San Francisco, instituted a ceremony in connection with commencement. In this ceremony, a distinguished physician from another school is asked to deliver an address and is presented with a gold-headed cane by Dr. Kerr. A gold-headed cane is also presented to an outstanding member of the senior class, with honorable mention given to two other senior students.

A similar ceremony was initiated this year at the commencement of the University of Colorado School of Medicine by James J. Waring, M.D., F.A.C.P., Professor of Medicine. Most fittingly, Dr. Kerr was selected to give the Baccalaureate Address and to join in making the first awards. The cane which Dr. Waring received from Dr. Kerr at the University of California in 1945 was presented to John G. Ryan, M.D., F.A.C.P., Associate Professor of Medicine in the University of Colorado, and a similar award was made to Kon Wyatt, Jr., Pueblo, Colo., who had been selected by the faculty from a list of names submitted by the graduating class. The title of Dr. Kerr's address was the "Immortality of Inspiration."

The American College of Radiology held a Past Presidents' Dinner in connection with its recent 25th Anniversary Meeting in Chicago. Among the past Presidents so honored were George E. Pfahler, M.D., F.A.C.P., who was the first President, and W. Edward Chamberlain, M.D., F.A.C.P., both of Philadelphia, Pa.

A partial list of speakers for the Annual Meeting of the Mississippi Valley Medical Society, which will be held at Springfield, Ill., on September 29 and 30 and October 1, 1948, under the Presidency of Willard O. Thompson, M.D., F.A.C.P., Chicago, Ill., includes the following members of the College: Anton J. Carlson, M.A.C.P., Lowell T. Coggeshall, F.A.C.P., Paul S. Rhoads, F.A.C.P., and John B. Youmans, F.A.C.P., all of Chicago; Arthur R. Colwell, F.A.C.P., Evanston, Ill.; and Raymond O. Muether, F.A.C.P., St. Louis, Mo.

The guest speakers for the Annual Fall Clinical Conference of the Kansas City Southwest Clinical Society include Howard T. Karsner, M.D., F.A.C.P., Cleveland, Ohio, William A. Sodeman, M.D., F.A.C.P., New Orleans, La., and Ignacio Chavez, M.D., F.A.C.P., Mexico, D. F., Professor of Medicine in the University of Mexico School of Medicine and Director of the National Institute of Cardiology of Mexico, at which institution the American College of Physicians offered a Postgraduate Course under Dr. Chavez's direction, August 2–13, 1948.

Colonel Otis O. Benson, Jr., (MC), USA, F.A.C.P., recently presented a paper at the Journées Médicales, in Brussels, Belgium. Colonel Benson is Chief of the Medical Research Division of the Office of The Air Surgeon in Washington, D. C.

Dr. George C. Griffith, F.A.C.P., Director of Postgraduate Medical Instruction in the University of Southern California, Los Angeles, is on a teaching tour of the South Pacific for the University and the U. S. Navy. He will visit Hawaii, Korea, Japan and South Pacific islands and will return during August.

North Dakota Regional Meeting, Fargo, N. D., September 11, 1948

The A. C. P. Regional Meeting for members and guests in North Dakota will be held at Fargo under the Governorship of R. B. Radl, M.D., F.A.C.P., on September 11 rather than September 18 as was announced earlier. William S. Middleton, M.D., F.A.C.P., Madison, Wis., 1st Vice President, will be the guest of honor. The local chairman for this meeting is A. C. Fortney, M.D., F.A.C.P.

OBITUARIES

DR. LEWIS GEORGE ALLEN

Dr. Lewis G. Allen, Kansas City, Kans., died May 28, 1948, at the age of fifty-seven. He received the A.B. and M.D. degrees from the University of Kansas in 1915 and 1917, respectively. He was a Ward Surgeon in the Medical Diagnostic Service at Base Hospital No. 1, Camp Travis, in World War I. Following the war, Dr. Allen entered private practice of Radiology in Kansas City, Kans. His staff appointments were to the Bethany, Providence and St. Margaret's Hospitals, and he was Professor of Clinical Roentgenology in the University of Kansas School of Medicine.

Dr. Allen was Past President of Wyandotte County Medical Society, Councilor of the Kansas Medical Society, Past President of the Kansas City Southwest Clinical Society, and an honorary member of the Kansas City Academy of Medicine. A Chancellor of the American College of Radiology, he was Past President of the Radiological Society of North America, and the Kansas City Radiological Society. Certified by the American Board of Radiology, Dr. Allen became a Fellow of the American College of Physicians in 1943.

In addition to his teaching and medical executive offices, Dr. Allen participated in many civic enterprises. He was Chief of the Emergency Medical Service under the Civilian Defense Program for Kansas City, Kans. He was a charter member of the Kiwanis Club, and a Trustee of the Blue Cross Hospital Service. He was also a member of the Board of Directors of the Blue Shield Medical Care, of which organization he was an early and enthusiastic organizer. He was a Trustee of the Boylan Foundation for Surgical Research.

Dr. Allen has, over a long period of time, given unselfishly of his services to organized medicine, both in teaching and in the various medical societies. Through his active medical life, it was the privilege and purpose of Dr. Allen to give more than his full share to the promotion of his chosen specialty, to the preservation of physician-patient relations through prepaid medical plans, and to the reorganization of his Alma Mater to its present highly respectable position as a center of medical education.

HAROLD H. JONES, M.D., F.A.C.P.,
Governor for Kansas

DR. M. WILLIAM CLIFT

M. William Clift was born in Bay City, Mich., in 1883. He attended Olivet College and received his degree in medicine from the University of Michigan in 1905. During his career he served as Radiologist to the Hurley Hospital, Flint, Mich., as Consulting Radiologist to the Michigan Home and Training School, Lapeer, and to the Midland Hospital, Midland, Mich. During World War I, Dr. Clift was Chief of Laboratory Service of Base Hospital No. 36, and Officer in Charge of the School of Roentgenology in Paris.

Dr. Clift was a fellow of the American Medical Association and a member of the Michigan State Medical Society, and the Roentgen Ray Society. He was elected a Fellow of the American College of Physicians in 1920.

His death occurred on May 7, 1948.

DR. WILLIAM DEVITT

William Devitt, M.D., was born in Philadelphia, September 18, 1874, and passed on to greater rewards on May 20, 1948, at his home in Allenwood, Pa.

Dr. Devitt received his M.D. in 1902 from Medico-Chirurgical College of Philadelphia and Sc.D. (Honorary) from Bucknell University in 1928. He was a diplomate of the American Board of Internal Medicine. He practiced internal medicine in Philadelphia from 1902 to 1914. He had one dream which he fulfilled with his own labor and time—DEVITT'S CAMP. This was established in 1912 and is said to house more than one hundred tuberculosis patients; and to it, from 1914, Dr. Devitt devoted full time as Physician in Charge. He also served as Consultant to the North Eastern Penitentiary, Lewisburg, Pa.

Dr. Devitt became a Fellow of the American College of Physicians in 1929. He was also a Fellow of the American Medical Association and a member of the Medical Society of the State of Pennsylvania, Lycoming County Medical Society, Medical Club of Philadelphia, National Tuberculosis Society, and American Academy of Tuberculosis Physicians. He was a past President of the American College of Chest Physicians and a former Director of the Pennsylvania Tuberculosis Society.

His passing will be a great loss to his friends and associates and to all those who benefited by his life work. In his memory may DEVITT'S CAMP continue aiding tuberculosis patients.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. FRED WILLIAM GAARDE

Dr. Fred William Gaarde was born in Minden, Nebr., on June 20, 1887, and died in Rochester, Minn., on February 10, 1948. He received his S.B. degree at the University of Chicago, 1909; and his M.D. from Rush Medical College in 1912. He practiced medicine in Chicago from 1913 to 1920. From 1914 to 1918 he was instructor in medicine in the Rush Medical College and assistant on the attending staff at Presbyterian Hospital. He was an assistant to Dr. Frank Billings. He was a diplomate of the American Board of Internal Medicine. He served as a Major in the Medical Corps of the American Expeditionary Force during World War I. In 1920 he became an assistant in medicine at the Mayo Clinic and assistant professor in medicine at the Mayo Foundation of the University of Minnesota. He later became head of the General Diagnostic Section and senior consultant in the Clinic and associate professor of medicine at the Foundation. He became a Fellow of the American College of Physicians in 1929. He was also a Fellow of the American Medical Association and member of the Minnesota State Medical Association and Olmsted-Houston-Fillmore-Dodge Counties Medical Society; also of the Institute of Medicine of Chicago, the Society of Internal Medicine of Chicago, the Central Clinical Research Club, Minnesota Society of Internal Medicine, Association for the Study of Allergy, Sigma Nu, Nu Sigma Nu, and Sigma Xi. At the Mayo Clinic Dr. Gaarde was considered one of the pioneers in the investigation and treatment of allergic conditions.

WESLEY W. SPINK, M.D., F.A.C.P.,
Acting Governor for Minnesota

DR. HOWARD BISHOP GARNER

Dr. Garner was born at Tyrone, Mich., October 30, 1866. He received the M.D. degree from the University of Michigan in 1892. During World War I he served in the Medical Reserve Corps of the United States Army with the rank of Captain. He practiced medicine for many years in Detroit, with offices in the David Broderick Tower. He retired from practice in 1945.

Dr. Garner was an active member of the Wayne County Medical Society, and

devoted a great deal of his time to serving on the Ethics Committee of this organization. He refused all other committee appointments. He became a Fellow of the American College of Physicians in 1922, and died on February 13, 1948.

DOUGLAS DONALD, M.D., F.A.C.P.,
Governor for Michigan

DR. EUGENE JOSEPH LEOPOLD

In the death of Dr. Eugene Leopold on January 14, the College has lost a staunch supporter. Dr. Leopold had been a Fellow of the College since 1931. He had long been active in the practice of internal medicine and the study of diabetes in Baltimore.

The son of Joseph and Rosa Leopold, Dr. Leopold was educated in the public schools of Baltimore and at Deichmann's School. He received the A.B. degree in 1901 and the M.D. degree in 1905, from Johns Hopkins University. Then followed postgraduate studies in Berlin, Munich and London from 1905 to 1907. He became an Instructor in Medicine in the Johns Hopkins University School of Medicine. He was Assistant Visiting Physician and Physician-in-Charge of the Diabetic Clinic of Johns Hopkins Hospital. He served as Visiting Physician and Chairman of the Medical Board of Sinai Hospital. During World War I Dr. Leopold served in the Medical Reserve Corps of the U. S. Army with the rank of Captain.

Dr. Leopold was a Fellow of the American Medical Association, and a member of the Medical and Chirurgical Faculty of Maryland, Southern Medical Association, Baltimore City Medical Society, American Association for the Advancement of Science, the American Tuberculosis Association, the American Association of Hospital Social Service.

WETHERBEE FORT, M.D., F.A.C.P.,
Governor for Maryland

DR. LEONARD GRUNER WEBER

Dr. Leonard G. Weber of New York City died in his seventieth year on November 30, 1947.

Dr. Weber was born in New York City, was a graduate of Columbia University College of Physicians and Surgeons in 1900. He served a residency in Lincoln Hospital and was associated later with the Lenox Hill Hospital and with the Manhattan Eye and Ear Hospital. Dr. Weber became a Fellow of the American College of Physicians in 1920 and was a member of the New York Athletic Club. He served in various capacities on the staff of the Lenox Hill Hospital and at the time of his death was a senior consultant in medicine at the Manhattan Eye and Ear Hospital.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. AUGUST WILLIAM FREDERICK WESTHOFF

Dr. August Westhoff, of Richmond Hill, N. Y., died on February 21, 1948. He was born in Philadelphia on August 1, 1866. He received his premedical education at New York University and received his medical degree from Bellevue Hospital Medical College in 1891. After graduation he served as pathologist at St. Catherine's Hospital, Brooklyn, from 1892 to 1913, and on the medical service at Wyckoff Heights Hospital from 1911, finally becoming Chief of the Medical Service from 1938 to 1947. He then became Director Emeritus. He was also Attending Physician at the Bethany Deaconess Hospital at the time of his death. Dr. Westhoff was a member of The

Medical Society of The State of New York and of the Medical Society of the County of Kings. A Fellow of the American Medical Association, he became a Fellow of the American College of Physicians in 1928.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. GEORGE AIKEN DOWLING

George Aiken Dowling was born at Little Valley, Minn., January 24, 1879, and died at his home in Seattle, Wash., on October 26, 1947.

He graduated from Northwestern University Medical School in 1905, and interned at Cook County Hospital, Chicago. In 1906 he visited his brother, the late Dr. Jay Thomas Dowling, in Seattle, and while there wrote the examination leading to the license to practice medicine and surgery. He then returned to Chicago to complete his postgraduate training, following which he opened his office for practice on April 1, 1907. Dr. Dowling gave most of his attention to diagnosis and internal medicine, although he enjoyed a considerable amount of general practice.

In 1919 Dr. Dowling became associated with the founders' group of the Virginia Mason Hospital and the Mason Clinic, which association continued until his retirement from practice because of ill health, in September, 1945.

From 1919 on his practice was limited to diagnosis and internal medicine. During these years his energetic interest in and wise counsel as secretary, concerning the affairs of the hospital, were invaluable during its years of growth and expansion.

Dr. Dowling was a Fellow of the American Medical Association, a member of the Washington State and King County Medical Societies, the Seattle Academy of Medicine, the North Pacific Society of Internal Medicine, and a diplomate of the American Board of Internal Medicine. He was elected to Fellowship in the American College of Physicians in 1926.

George Dowling, in addition to being a well trained and most competent and conscientious physician, was a good citizen, and never failed to give his support to all civic enterprises aimed at making Seattle a better place in which to live. He was an unusually well balanced individual. When confronted with problems, his solution was not offered until after due consideration. He was always fair in his viewpoint to an extreme degree, and was ever capable of seeing both sides of a controversy.

He will long be missed by his family, his colleagues and the profession, his many patients, and most particularly by his immediate associates at the Virginia Mason Hospital.

LESTER J. PALMER, M.D., F.A.C.P.

DR. GRANT ORANTE FAVORITE

Dr. Grant Orante Favorite, distinguished citizen and man of medical science, was born in Ortucchio, Italy, June 20, 1903. He came to the United States of America in 1912. In 1925 he obtained his Bachelor of Science degree from Hahnemann Medical College and Hospital of Philadelphia, where he also acquired the degree of Medical Doctor in 1927. Dr. Favorite received the Master of Public Health degree from the University of Pennsylvania in 1944. A diplomate of the American Board of Pathology, Dr. Favorite was Assistant in Pathology in the Hahnemann Medical College and Hospital of Philadelphia, 1928–29, and subsequently became Instructor and Associate Professor of Pathology and Bacteriology, and Professor of Bacteriology and Head of the Department of Preventive Medicine and Public Health. In 1944 he became Associate in Bacteriology and Immunology, Jefferson Medical College of Philadelphia. Dr. Favorite was a major in the Army of the United States in 1942.

Dr. Favorite was a member of the Society for Experimental Biology and Medi-

cine, American Society of Clinical Pathologists, Society of American Bacteriologists, American Association of Immunologists, American Public Health Association, Pathological Society of Philadelphia, Medical Club of Philadelphia, The Medical Society of New Jersey, Camden County Medical Society, Homeopathic Medical Societies of the County of Philadelphia and State of Pennsylvania, and a Fellow of the American Medical Association. He became a Fellow of the American College of Physicians in 1934, and a Life Member. He died May 4, 1948.

Dr. Favorite's fascinating personality, diplomatic mannerisms, and brilliant mind are a great loss to the entire medical profession.

EDWARD LEROY BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. SAMUEL JOHNSTON

Dr. Samuel Johnston died suddenly at his home in Toronto on April 14, 1947, following a coronary occlusion at the age of 78.

Dr. Johnston was born in Ontario and received his early education in Guelph Collegiate Institute. He graduated from Trinity Medical School in 1901 and interned in the Toronto General Hospital. He early developed a special interest in anesthesiology and in 1910 went abroad for postgraduate study in this field. On his return, he devoted himself to the practice and teaching of this subject, and became Chief Anesthetist to the Toronto General Hospital. He was a past president of the American Association of Anesthetists, and first president of the Canadian Society. He was chairman of the Section of Anesthesia of the British Medical Association at the Nottingham meeting in 1926.

Dr. Johnston was a Charter Fellow of the Academy of Medicine of Toronto and was President in 1942–43. He was a member of the Rotary and Empire Clubs. In 1904 he married Dr. Margaret Macallum who survives him. He was admitted to Fellowship in the American College of Physicians in 1924.

Dr. Johnston is mourned by a host of friends, both in and out of the medical profession. Of a genial and kindly disposition he inspired a large group of students and graduates, and the foundation stone of the new edifice of Anesthesiology indelibly bears his mark.

H. K. DETWEILER, M.D., F.A.C.P.,
Governor for Ontario

DR. WILLIAM MOSER

Dr. William Moser, F.A.C.P., of Brooklyn, died September 12, 1947. He was born in New York City in 1868, received his medical training at New York University Medical College and the University of Berlin. He served as pathologist and as physician at St. Catherine's Hospital, as pathologist at St. Mary's Hospital, and as physician at the Wyckoff Heights Hospital. He was elected a Fellow of the American College of Physicians in 1920.

DR. WESLEY H. WALLACE

Dr. Wesley H. Wallace, F.A.C.P., of Brooklyn, N. Y., died on October 14, 1947. He was born in Alexandria Bay, N. Y., November 9, 1869; received his medical degree from the Medical College of Virginia in 1899, and was formerly Instructor in Radiography at the Long Island College Hospital. He had been Attending Radiologist at the Methodist Hospital and Coney Island Hospital. He served during World War I in the Third Field Hospital Unit of the New York National Guard. He was at one time Vice President of the Radiological Society of North America and had been a Fellow of the American College of Physicians since 1920.

DR. SAMUEL HUMES WATSON

Samuel Humes Watson was born at Vinton, Iowa, March 15, 1877. He received his medical degree from Rush Medical College in 1899. Dr. Watson served as Medical Director of the Tucson-Arizona Sanatorium from 1911–18. Other appointments which he held were: Medical Director, St. Luke's in the Desert; Physician in Chief, Barfield Sanatorium; Attending Physician, Chief of Staff, Chairman and Member of Executive Committee, St. Mary's Hospital and Sanatorium; Medical Director, Anson Rest Home for Tuberculosis. He served as former President of the Pima County, Arizona State and Arizona Anti-Tuberculosis Associations; Vice President, American Association for the Study of Allergy; Director, National Tuberculosis Association. A member of the American Sanatorium Association, and the Medical and Surgical Association of the Southwest, and a Fellow of the American Medical Association, Dr. Watson was elected a Fellow of the American College of Physicians in 1923.

Dr. Watson will long be remembered by his colleagues and his patients for his great strength of conviction and for his feeling of responsibility to his patients. Very early, and throughout his period of activity, he championed the importance of bed rest in tuberculosis. He commanded the respect of both his superiors and his subordinates. His passing will be mourned by many.

W. R. Hewitt, M.D., F.A.C.P.

ABSTRACT OF MINUTES OF THE BOARD OF GOVERNORS

SAN FRANCISCO, CALIF.

APRIL 21, 1948

The second meeting of the Board of Governors was called to order at 1:00 p.m. on April 21, 1948, with Dr. Walter L. Palmer, Chairman, presiding, and Mr. E. R. Loveland acting as secretary. Present as guests were Dr. Hugh J. Morgan, President of the College, and Dr. A. B. Brower, a member of the Board of Regents.

Dr. Palmer read a telegram of greeting from Dr. Chauncey W. Dowden, former Chairman of the Board. The Secretary called the roll and recorded the presence of 41 governors and 15 alternates. The newly elected governors were welcomed by the Chairman.

There was considerable discussion of the immediate responsibility of the governor in the endorsement of candidates for Associateship and Fellowship in the College. Regent Brower, former Governor of Ohio, who had made a particular study of this problem, attended the meeting and spoke on the procedure developed by him and emphasized the importance of the governor getting in touch with members of the College in his area in order to ascertain their exact feeling with regard to the nominees. The governor then should summarize his study in each instance and send this to the Committee on Credentials.

Dr. Benjamin F. Wolverton, in the absence of Dr. Edgar V. Allen, Chairman of the committee appointed at the annual session in 1947 to study the method of election of governors, made the following report: "The selection of nominees for the Board of Governors shall be made after due consideration of suggestions of members from the respective states, provinces or districts which will be represented by the nominees, if elected."

"The By-Law does not specify how many or which members shall be consulted by the Nominating Committee, nor by what method. This Committee believes that each and every member should have an opportunity to express his preference for Governor. It also believes that this expression or preference by all members of a given state or constituency should merely serve as a guide for the Nominating Committee, and should not be binding on the Committee to nominate the member receiving the most votes. It is conceivable that, in some instances, the member receiving the most votes would not be a desirable Governor.

"In view of these and many other considerations which have been discussed by the Committee, we offer the following plan and recommend its adoption:

"Each year, when the candidate lists are mailed to the membership, those going to the state or constituencies whose Governor's terms are about to expire shall be accompanied by a suitable form on which the members may state their preference for Governor. On the return of these forms to the office of the Executive Secretary, the names offered and the number of votes for each shall be listed and given to the Nominating Committee, to be taken into consideration in making its nominations."

The adoption of the report was moved by Dr. Wolverton and seconded by Dr. Asa L. Lincoln. After extensive and lively discussion Dr. Wallace M. Yater moved as an amendment to the resolution a suggestion made by Dr. Flinn that the new governor be elected one year in advance in order that he might serve as "Governor-Elect" and thereby be enabled to learn from the retiring governor some of the details. Dr. Flinn seconded the amendment.

Mr. Loveland presented a detailed statement of the functioning of the Nominating Committee, emphasizing the fact that serious study is made of each situation and an effort made to obtain the man best fitted for the position rather than the most popular one.

Dr. Donald moved a second amendment to the resolution suggesting that the Nominating Committee be requested to send to the Fellows in the district in which the new governor is to be elected the names of three to five individuals with the request that they indicate their preference. The results of this policy would serve to guide the Committee. The amendment was seconded by Dr. Yater. The amendment was put to a vote and lost, there being 8 in favor and 32 opposed. Dr. Yater's amendment for the election of Governors one year in advance of their taking office was put to a vote and was lost.

The original resolution was put to a vote and lost, the vote being 10 in favor and 32 opposed.

Dr. Cason nominated Dr. Robert Wilson, Jr., from South Carolina to succeed Dr. J. Edwin Wood, Jr., resigned, as a member of the Committee on Credentials. Dr. Yater moved that the nominations be closed. Dr. Flinn seconded the nomination, and the vote was unanimous.

Mr. Loveland distributed copies of the financial reports of the College for the past year and gave a brief analysis.

In behalf of the Credentials Committee Dr. Yater made the following statement: "There are two entirely different items to be considered:

"(1) The Committee realizes that the number of applicants for admission is growing steadily. The question comes up from time to time about a candidate who is not an internist, but is a neuropsychiatrist, a dermatologist, or some other affiliated specialist. The informative booklet of the College says that membership need not be made up only of internists, but may include those properly qualified in pediatrics, neurology, psychiatry, public health, radiology, and so forth.

"The Committee believes it would be well seriously to consider changing our regulations and limiting membership in this organization to those who are internists and to discontinue after a certain time to take in men who are not internists, even though they be engaged in affiliated specialties.

"The Committee makes this recommendation primarily to further limit the size of the College. These affiliated specialties all have their own certifying boards and their own special societies, and the Committee questions whether radiologists, dermatologists, and a few others, ever take a very vital interest in the College. They are amiable and distinguished people who are in purely scientific branches, a little different from strict internal medicine."

Upon motion by Dr. Yater and seconded by Dr. R. R. Snowden, it was moved that this recommendation be approved and recommended for adoption to the Board of Regents, and the matter was opened for discussion. After protracted discussion the motion was put to a vote and lost, there being 10 in favor and 34 opposed.

Dr. Yater then presented the second part of the recommendations of the Credentials Committee as follows:

"(2) In spite of explanatory and clear definitions which the Survey Committee made and were incorporated as amendments to our By-Laws last year, it is still a very difficult matter from data available to come to a conclusion as to who is an internist, and whether he is a man who will ultimately be able to attain certification. Even those members of the Credentials Committee who were most violent in their opposition to the recommendations some of us made, namely, that before a man should be considered as an Associate he should be certified by the American Board of Internal Medicine, have come to the conclusion that such a rule wouldn't be too objectionable, after all, if we could limit the membership of the College to those who are internists. If we decide to take only internists, we can only recognize those who have already been certified, and many difficulties would be solved and hours of debate would be eliminated. The Committee feels that it would make for a much stronger and more homogeneous organization."

Dr. Yater moved and Dr. Alex. M. Burgess seconded the adoption of this recommendation. After spirited discussion the motion was put to a vote and lost, there being 10 in favor and 30 opposed.

Dr. Cason made the following motion:

"(1) That we recommend to the Board of Regents that a committee be appointed to study the question of the approach to accepting Associates;

"(2) to study the advisability of extending the number of years of Associateship;

"(3) to study any method that may be devised by which the standards required to become a Fellow can be raised through which the size of the College may be properly limited;

"(4) to consider the question of eliminating Associateship. That is just to be considered and this committee ought to be empowered to make a careful and complete study. If it takes the committee two years to bring in a report, all right, but it should make a comprehensive study of what our ills are and what we need to do."

The motion was seconded by Dr. Yater and, after some discussion, was carried unanimously.

Dr. Burgess, in order to obtain an expression of opinion on the part of the Governors, moved that it is the present sentiment of the Board of Governors, that the Associateship should eventually be eliminated. The Chairman ruled that this was a request for an expression of sentiment. Twenty-seven hands favored the suggestion and 14 opposed it.

Mr. Loveland discussed with the Governors the proposed sites for the 1949 and 1950 meetings.

In closing the Chairman expressed his regret that several governors who had given the College a long and distinguished service could no longer qualify for re-election, as a result of the introduction of the regulation limiting the term of governors. In behalf of the Board he expressed great appreciation to these men: Dr. Flinn of Delaware, Dr. Cason of Florida, Dr. Levy of Texas, Dr. Hitchcock of Montana, Dr. Holmes of Arizona, Dr. Giddings of Georgia, Dr. Dowden of Kentucky, Dr. Drake of Maine, Dr. Suarez of Puerto Rico. A rising vote of appreciation was given to the retiring members and the meeting adjourned at 3:10.

WALTER L. PALMER, *Chairman,*
Board of Governors
E. R. LOVELAND, *Secretary*